

31.1 Introduction

■ Generalized Considerations

● *Biochemical and Clinical Heterogenicity*

The porphyrias result from inherited deficiencies in one of the seven enzymes of heme biosynthetic pathway (Fig. 31.1) [1]. Heme synthesis is most prominent in two organs, in bone marrow and liver. Therefore, porphyrias are classified as *hepatic porphyrias* or as *erythropoietic porphyrias* according to the tissue of excess porphyrin production.

Another classification scheme of the porphyrias is more supportive of the clinical diagnosis and treatment, as it is based on the two major symptoms of the porphyrias, the first being acute attacks of abdominal pain and the second photosensitivity. The first group will be called *acute porphyrias* (Fig. 31.2), the second one *cutaneous porphyrias* (Fig. 31.3). Two of the porphyrias, that may cause both symptoms, belong to the acute porphyrias.

The *more frequent porphyrias* (Table 31.1) begin only after puberty except for erythropoietic protoporphyria (31.7). Symptoms in the latter may be seen from infancy or early childhood. These frequent porphyrias are all autosomal dominant diseases with incomplete penetrance. That means that although the enzymatic defect can be traced among 50% of direct relatives, only a minority of them become symptomatic and the overt diseases often appear to be sporadic.

The *rare porphyrias* with an autosomal recessive inheritance, mostly are symptomatic in the neonatal or even in the prenatal period. Generally, their symptoms are more severe than those of the autosomal dominant forms. Some variant porphyrias resulting from combined forms (e.g. inheritance of porphyria variegata and of porphyria cutanea tarda) or from homozygous inheritance of otherwise heterozygous porphyrias (homozygous porphyria variegata) [2] have been described in a few case reports.

● *Diagnosis and Screening Policy [1]*

All but one porphyria lead to increased urinary porphyrin excretion in symptomatic individuals, thereby the pattern of the porphyrins varies in dependence of the underlying defect. Excess porphyrin precursors, aminolevulinic acid (ALA) and porphobilinogen (PBG) in urine are present in the acute porphyrias only.

The only porphyria with a normal urinary profile is erythropoietic protoporphyria (31.7). Its clinical picture differs from the other porphyrias and it is reliably diagnosed by increased protoporphyrin concentrations in the erythrocytes.

In the acute porphyrias, symptomatic and latent phases alternate, and during the latter, biochemical abnormalities may be only minor or even absent. Therefore, in questionable cases porphyrin precursors and porphyrins should be assessed in a urine specimen collected during a symptomatic period that allows one to prove or exclude the diagnosis.

● *Therapeutic Modalities [3]*

As outlined above, most porphyrias have a low penetrance. Additional factors (drugs, alcohol, hormones and fasting) are factors precipitating disease expression. Therefore, the first therapeutic action is to eliminate these factors. The second measure is to block the synthesis of excessive heme precursors, and the third one is to prevent photosensitivity.

■ The Four Acute Porphyrrias

The three autosomal dominant diseases, acute intermittent porphyria (31.2) [1, 4], variegate porphyria (31.6) and hereditary coproporphyria (31.5) share a common symptomatology (Tables 31.3.1/31.3.2). Affected individuals suffer from acute attacks of severe, colicky, abdominal pain, mostly of several days duration and combined with nausea, vomiting, obstipation and subileus. Tachycardia and hypertension is often present too. Within a few days these symptoms may spontaneously subside or they may progress as well to a predominant motor neuropathy, disturbance of electrolyte balance (hyponatremia, hypomagnesemia), seizures, confusion and coma.

The first disease manifestation is rarely before puberty, the first maximum is in the young adults and a second in senescence. Females are 5–10 times more often symptomatic than males and often show spontaneous symptomatology in the premenstrual days. The rare autosomal recessive acute porphyria (ALA-dehydratase deficiency, 31.1) may become symptomatic shortly after birth in the neonatal period or late after puberty with the same symptoms as other acute porphyrias (Table 31.2).

Laboratory examinations reveal significantly i.e. more than 5, often 10–20 times increased urinary porphyrin precursors (ALA and PBG) during an

acute attack in all three acute autosomal dominant forms accompanied by excess urinary porphyrins. Normal or only slightly elevated values of ALA and PBG (up to two times upper limit of normal) during a symptomatic period virtually exclude the diagnosis of an acute porphyria. Only ALA and urinary coproporphyrin III isomer are abnormally high in autosomal recessive ALA-dehydratase deficiency.

Differential diagnosis of the firstly mentioned three acute porphyrias is attained by the analysis of the fecal porphyrin pattern and by measurement of PBG-deaminase activity in red blood cells (Fig. 31.2). *Acute intermittent porphyria* is characterised by decreased PBG-deaminase activity, and normal or only slightly increased fecal porphyrins, with characteristic ratio of coproporphyrin I isomer to III being >1.0 . *Hereditary coproporphyria* exhibits a significant increase in fecal coproporphyrins with coproporphyrin III being the dominant isomer. Both fecal coproporphyrin III and protoporphyrin are increased in *variegate porphyria*.

Treatment: As outlined above the first measure is to eliminate any factors that provoke porphyric symptoms. Precipitating factors are drugs including the non prescription ones, stress, infections, alcohol excesses, and hormonal changes. In acute porphyrias, these factors are often drugs that lead to hepatic enzyme induction and by this increasing the demand for heme, as heme is the prosthetic group of the drug metabolising cytochrome P450. Lists of harmful as well as safe drugs in the acute porphyrias are available on the internet [5, 6]. Glucose has an inhibitory effect on the first and rate limiting enzyme of heme biosynthesis, the ALA synthase. The same has been shown for the end product of heme synthesis, the heme itself. High dose of glucose infusions (200–500 g/d) have been used to interrupt acute porphyria symptoms, but with a limited efficacy. Therefore, early (within 24–48 hours after hospital admission) application of heme, either heme arginate or panhematin 3–4 mg/kg per day, has been advocated. If it is solubilised in a 4 or 20% human albumin solution in an equimolar concentration, side effects of the substance are reduced. Biochemical improvement is dramatic shortly after institution of heme infusions and abdominal pain usually subsides within 2–3 days.

Family screening: As mentioned above, all three acute porphyrias are autosomal dominant diseases. 50% of direct relatives are also carrier of the defect allele and are prone to symptoms, if exposed to drugs and other stressors. Family screening and instruction of all affected individuals to avoid precipitating factors is therefore strongly recommended. Different laboratory tests are used for family screening in the three acute porphyrias:

Acute intermittent porphyria: Mutation analysis has been shown to be 5–15% more reliable than enzymatic and biochemical screening [4]. The mostly “private” (family specific) mutation of the PBG-deaminase gene should be identified firstly in the index patient and then the relatives are to be tested for the presence or absence of this mutation [7].

In *variegate porphyria*, plasma is analysed for the presence of a specific fluorescence emission peak at 626 nm, that is thought to be the most sensitive test for latent mutation carrier detection besides the DNA analysis, which has just recently become available [8, 9]. In the case of *hereditary coproporphyria*, fecal porphyrin analysis is the best available test, but with an unknown sensitivity. Also here, there is limited experience with DNA analysis that is conducted in a few specialized laboratories recently [10].

■ The Cutaneous Porphyrrias [1]

Skin affection in the porphyrias is restricted to light exposed areas e.g. face, back of hands and eventually feet (especially in females). Treatment of all forms of photosensitivity is to avoid light exposure and additionally to block it by reflecting sun creams, containing titanium oxide. Solely UV-absorbing sun creams do not help as the damage producing, maximal excitation wavelength of porphyrins is in the visible region (at 404 nm).

Two forms of photosensitivity can be distinguished: either the development of skin blisters of 1–2 cm diameter accompanied by skin fragility, scarring, hyperpigmentation and eventually hirsutism or acute and severely painful photodermatosis with pale swelling of affected skin areas.

Skin blisters are seen in *porphyria cutanea tarda* (31.4), *porphyria variegata* (31.6) and *hereditary coproporphyria* (31.5). The last two belong to the acute porphyrias mentioned above. It is to emphasize that individuals affected with one of the two acute porphyrias may not suffer from abdominal pain at all, but only from skin lesions that are neither clinically nor histologically different from those of PCT. Biochemical analysis of both, urine and feces, is sufficient for differential diagnosis (p. 608, Fig. 31.2). The differentiation is important because of differing treatment strategies. PCT patients excrete large amounts of porphyrins in urine with a dominance of uro- and heptacarboxyporphyrins. The precursors are normal or only slightly elevated (less than two times upper limit of normal). Excess uro-, hepta- and hexacarboxyporphyrins are excreted also in feces and – pathognomonically – isocoproporphyrin is present. Often concomitant liver disease or liver hemosiderosis is the precipitating factor of this porphyria. Elimination of eventual alcohol overconsumption, and 2–4 weekly phlebotomies are required until hepatic iron deposits are reduced. In severe cases, low dose chloroquine (2×125 mg/week) can be added.

The most severe porphyrias with cutaneous symptomatology are the two autosomal recessive forms, congenital erythropoietic porphyria (31.3) and hepatoerythropoietic porphyria (31.8). Both disorders show a great variability of disease course, that varies from intrauterine “hydrops fetalis” with severe hemolytic anemia, over neonatal onset with red urine, prolonged hyperbilirubinemia and acute severe skin lesions induced by phototherapy, up to the relatively benign forms with late onset not before adult life. The

more severe forms have a transfusion-dependent anemia, skin-blisters, skin fragility, infections and scarring leading to mutilations and severe disfigurement of the face. In the severe forms with early onset, bone marrow transplantation is curative and should be discussed with an expert in porphyria. Other treatments have been proposed as effective in single cases, but were of no validity in others [11].

Acute painful photodermatosis with edema of the face, back of hands and eventually feet is the main symptom in erythropoietic protoporphyria (31.7) [12], but may also be observed in CEP (31.3) as a variant. Diagnosis of EPP is straight forward, as symptomatic patients always have increased free protoporphyrin above 6 μmol , being in most cases in the range between 15–50 μmol per liter of erythrocytes. Symptoms are reduced by minimising light exposure. Oral betacarotene is effective in about one third of the patients. Others profit from phototherapy by long wave UV, that must be applied only for some minutes. In a small portion of about 2–5% of affected individuals, subacute or acute liver failure develops due to accumulated protoporphyrins. A recent study revealed a phenotype-genotype correlation, in that EPP-patients with a missense mutation of the ferrochelatase have a decreased risk for this severe, life-threatening complication in comparison to other forms of mutations, called “null-allele” mutations [12]. Exogenous factors such as alcohol overconsumption or viral hepatitis may also contribute to this severe complication.

■ The Variant Porphyrias

In South Africa where both, porphyria variegata and porphyria cutanea tarda, have a relatively high prevalence, rare combined forms of these two porphyrias have been described. In addition, homozygous forms of otherwise heterozygously inherited porphyrias have been described of variegate porphyria and acute intermittent porphyria. These forms are characterized by severe symptoms not confined to porphyrin metabolism but including mental retardation and malformations. In erythropoietic protoporphyria, homozygosity has been claimed as the cause of fatal liver complication [13]. But this hypothesis was disapproved by enlarged studies [12, 14].

31.2 Nomenclature

No.	Disorder	Abbreviation	Synonym(s)	Inheritance	Affected enzyme (inheritance)	Chromosomal location	MIM
31.1	ALA-dehydratase deficiency	ALAD-D	Doss porphyria	Autosomal recessive	Aminolevulinate dehydratase	9q34	125 270
31.2	acute intermittent porphyria	AIP	Hydroxymethylbilane synthase deficiency, intermittent acute porphyria, PBG-deaminase deficiency, Swedish porphyria	Autosomal dominant	Hydroxymethylbilane synthase (syn.: uro(porphyrinogen-) synthase, Porphobilinogen-deaminase)	11q23.3	176 000
31.3	congenital erythropoietic porphyria	CEP	Günther's disease, Uro-cosynthase deficiency, Uroporphyrinogen-III-synthase deficiency	Autosomal recessive	Uroporphyrinogen-Cosynthase	10q25.2-q26.3	263 700
31.4	Porphyria cutanea tarda	PCT		Autosomal dominant	Uroporphyrinogen-decarboxylase (heterozygote)	1p34	176 100
31.5	Hereditary coproporphyria	HC		Autosomal dominant	Coproporphyrinogen-oxidase	3q12	121 300
31.6	Porphyria variegata	PV	Variegate porphyria, South African porphyria	Autosomal dominant	Protoporphyrinogen-oxidase	1q22	176 200
31.7	Erythropoietic protoporphyria	EPP	Hepatoerythropoietic protoporphyria, protoporphyria	Autosomal dominant	Ferrochelatase	18q21.3	177 000
31.8	Hepatoerythropoietic porphyria	HEP	Homozygous PCT	Autosomal recessive	Uroporphyrinogen-decarboxylase (homozygous)	1p34	176 100
31.9	Variant porphyria(s) unclassified				Combined heterozygous defects, homozygous forms of normally heterozygous porphyrias		

31.3 Metabolic Pathway

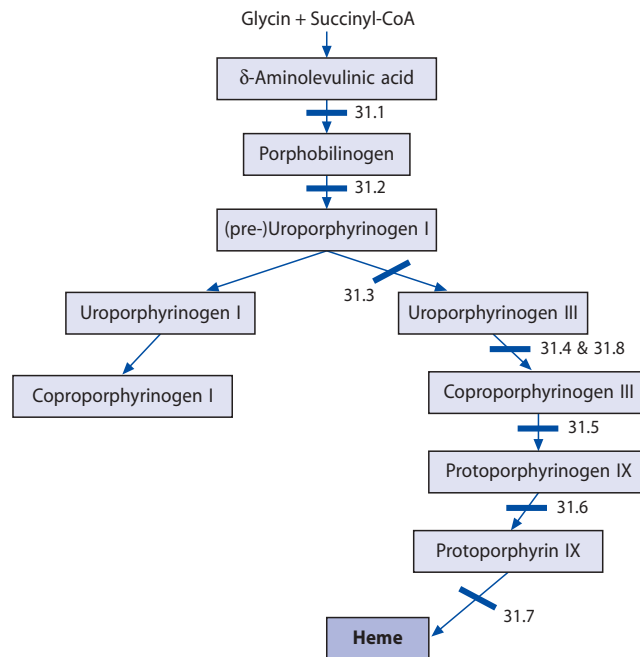


Fig. 31.1. Metabolic pathway of heme biosynthesis

31.4 Signs and Symptoms

Table 31.1. Overview on Symptomatology

No.	Disorder	Leading clinical symptoms	Onset of symptoms (maximum of first manifestation)	Frequency
31.1	ALA-dehydratase deficiency	Acute attacks	Neonatal periode	Very rare
31.2	Acute intermittent porphyria	Acute attacks	After puberty (adolescence and senescence)	Relatively frequent (1:10,000–100,000)
31.3	Congenital erythropoietic porphyria	Cutaneous (severe): blisters, rarely burning pain, mutilations	Neonatal periode (late onset possible)	Very rare
31.4	Porphyria cutanea tarda	Cutaneous: blisters, skin fragility	Often second half of life, both familial and sporadic cases	Relatively frequent
31.5	Hereditary coproporphyria	Acute attacks and/or cutaneous (blisters, skin fragility)	After puberty (adolescence and senescence)	Relatively frequent
31.6	Porphyria variegata	Acute attacks and/or cutaneous (blisters and skin fragility)	After puberty (adolescence and senescence)	Relatively frequent
31.7	Erythropoietic protoporphyria	Cutaneous (acute burning pain)	Infancy/childhood	Relatively frequent
31.8	Hepatoerythropoietic porphyria	Cutaneous (blisters, skin fragility, mutilation)	Neonatal period, infancy, childhood	Very rare
31.9	Variant porphyria(s) unclassified	Acute attacks and/or cutaneous	Variable	Rare

Table 31.2. δ -Aminolevulinic acid dehydratase deficiency (31.1) during acute attacks

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Attacks of severe crampy abdominal pain or seldom only muscular pain in proximal limbs	±	±	±	+	+
GI	Nausea, vomiting	±	±	±	+	+
	Obstipation, (sub-)ileus	±	±	±	+	+
Cardiovascular	Hypertension, tachycardia	±	±	±	+	+
CNS	motorneuropathy	±	±	±	+	+
	hyperaesthesia	±	±	±	+	+
	seizures	±	±	±	+	+
	coma	±	±	±	+	+
Electrolyte	Hyponatremia	±	±	±	+	+
	Hypomagnesiemia	±	±	±	+	+
Routine lab tests	Urine colour red-brown with pink fluorescence	±	±	±	+	+
Special laboratory	Urine 24 h: ALA grossly elevated (>5 times upper normal), PBG normal	±	±	±	+	+
	Urine 24 h: only coproporphyrin III significantly elevated	±	±	±	+	+
	Erythrocytes: ALA-dehydratase residual activity a few % of normal	±	±	±	+	+

Table 31.3.1. The acute porphyrias, acute-intermittent porphyria (31.2), porphyria variegata (31.6) and hereditary coproporphyria (31.5), during acute attacks

System	Symptoms/markers ^a	Adolescence ^b	Adulthood ^b
Unique clinical findings	Attacks of severe crampy abdominal pain or seldom only muscular pain in proximal limbs	+	+
GI	Nausea, vomiting	+	+
	Obstipation, (sub-)ileus	+	+
Cardiovascular	Hypertension, tachycardia	+	+
CNS	Motorneuropathy	±	±
	Hyperaesthesia	±	±
	Seizures	±	±
	Coma	±	±
Electrolyte	Hyponatremia	+	+
	Hypomagnesiemia	±	±
Skin	Blisters, fragility	± ^f	± ^f
Routine lab tests	Falsely positive urobilinogen in urine stix ^c	+	+
	Qualitative porphobilinogen in urine pos. ^c	+	+
	Urine colour red-brown with pink fluorescence ^d	+	+
Special laboratory	Urine 24 h: ALA, PBG grossly elevated (>5 times upper normal)	+	+
	Urine 24 h: All porphyrin fractions (uro-, heptac-, hexac-, pentac-, coproporphyrin) significantly elevated ^e	+	+

^a Acute porphyrias are rarely symptomatic before puberty.

^b Typical clinical and laboratory signs are only present in acute attacks, females are more likely to develop overt clinical disease.

^c Positive test results *must* be confirmed by quantitative analysis of porphyrin precursors in a 24-h urine sample.

^d Positive test results *must* be confirmed by quantitative analysis of porphyrins in a 24 hour urine sample.

^e Urinary porphyrin pattern is not useful to differentiate between the different forms of acute porphyrias: differential diagnosis see p. 604.

^f No skin affection in AIP (31.2), inconstant skin affections in PV (31.6) and HC (31.5).

Table 31.3.2. The acute porphyrias, acute-intermittent porphyria (31.2), porphyria variegata (31.6) and hereditary coproporphyria (31.5), during latent phases

System	Symptoms/markers ^a	Adolescence	Adulthood
Unique clinical findings	Attacks of severe crampy abdominal pain or seldom only muscular pain in back and proximal limbs	n	n
GI	Nausea, vomiting	n	n
	Obstipation, (sub-)ileus	n	n
Cardiovascular	Hypertension, tachycardia	n	n
CNS	Motorneuropathy	n	±
	Hyperaesthesia	n	n
	Seizures	±	±
	Coma	n	n
Electrolyte	Hyponatremia	n	n
	Hypomagnesemia	n	n
Routine lab tests	Falsely positive urobilinogen	±	±
	Qualitative porphobilinogen in urine pos.	±	±
	Urine colour red-brown with pink fluorescence	±	±
Special laboratory	Urine 24 h: ALA, PBG elevated	±	±
	Urine 24 h: All porphyrin fractions (uro-, heptac-, hexac-, pentac-, coproporphyrin) significantly elevated ^b	±	±

^a Acute porphyrias are not symptomatic before puberty.

^b Urinary porphyrin pattern is not useful to differentiate between the different forms of acute porphyrias: differential diagnosis see p. 605.

Table 31.4. Congenital erythropoietic porphyria (31.3) and hepatoerythropoietic porphyria (31.8)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Skin blisters, skin fragility, scarring and mutilation limited to light-exposed areas, disfiguration of the face	n	±	±	±	+
Hematology	Microcytic, hypochromic hemolytic anemia	±	±	±	±	+
Routine lab tests	Urine colour red-brown with pink fluorescence ^a	±	±	±	±	+
Special laboratory	Urine 24 h: total porphyrins grossly and constantly elevated	±	±	±	±	+
	Urine 24 h: main fraction are I-isomers (CEP) or uro- and heptacarboxyporphyrins (HEP)	±	±	±	±	+
	Blood plasma: same porphyrin pattern as in urine	±	±	±	±	+

^a Excitation wavelength long UV (eg 360 nm).

Table 31.5. Porphyria cutanea tarda (31.4)

System	Symptoms/markers	Adolescence	Adulthood ^b
Unique clinical findings	Skin blisters, skin fragility limited to light-exposed areas	±	+
GI	Concomitant liver disease (chronic HCV-infection, alcoholic liver disease, hemosiderosis of the liver)	±	+
Routine lab tests	Urine colour red-brown with pink fluorescence ^a	±	+
Special laboratory	Urine 24 h: total porphyrins grossly and constantly elevated	±	+
	Urine 24 h: main porphyrin fractions are uro- and heptacarboxyporphyrins	±	+
	Blood plasma: same porphyrin pattern as in urine ^c	±	+

^a Excitation wavelength at long UV (eg 360 nm).

^b Often onset in second half of life. Familial cases earlier.

^c Especially useful in patients on chronic hemodialysis that is a precipitating factor of PCT, but also of the clinically similar disease pseudoporphyria with no increase in plasma porphyrins.

Table 31.6. Erythropoietic protoporphyria (31.7)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Acute painful photodermatitis, edema limited to light-exposed areas (face, back of hands and feet)	n	±	±	+	+
GI	Complicating liver disease	n	n	±	±	±
Hematology	Slight microcytosis, slight anemia, low serum iron and serum ferritin	n	±	±	±	+
Special laboratory	Erythrocytic protoporphyrin: free protoporphyrin elevated	?	+	+	+	+
	Feces: protoporphyrin elevated	n	±	±	+	+

31.5 Reference Values

■ Urinary Porphyrin Excretion in Childhood (nmol Porphyrin/mmol Creatinine)

Age years	Uroporphyrin		Coproporphyrin I		Coproporphyrin III	
	mean	mean + 2 SD	mean	mean + 2 SD	mean	mean + 2 SD
0	7.28	14.3	17.1	35.7	7.05	22.8
0.25	3.74	18.3	8.36	24.7	12.2	34.4
0.5	2.72	18.1	5.79	12.2	12.6	34.9
0.75	2.40	6.84	6.27	12.5	14.8	44.0
1.0	2.23	6.03	6.27	14.0	19.7	52.0
1.5	3.06	9.94	6.04	14.5	18.4	49.4
2.25	2.48	5.76	5.78	15.5	15.8	44.1
3	2.62	6.42	5.01	13.5	10.6	33.1
4	1.90	5.72	4.23	10.4	11.0	36.3
6	1.90	5.72	4.23	10.4	11.0	33.5
9	1.80	4.26	3.73	8.09	6.74	21.8
15	2.23	7.31	3.90	7.92	6.98	23.7

■ Urinary Porphyrin Excretion in Adults [1]

Analyte	24 hour Value	Related to creatinine
ALA	<50 μmol	<2.5 $\mu\text{mol}/\text{mmol}$
PBG	<9 μmol	<1.5 $\mu\text{mol}/\text{mmol}$
Uroporphyrin	<60 nmol	<3.9 nmol/mmol
Coproporphyrin I	<100 nmol	<8.4 nmol/mmol
Coproporphyrin III	<200 nmol	<17.8 nmol/mmol

■ Fecal Porphyrin Excretion [1]

Analyte	Upper limit of reference
Coproporphyrin I	<20 nmol/g
Coproporphyrin III	<12 nmol/g
Protoporphyrin XI	<80 nmol/g

■ Erythrocytic Porphyrins^a

Analyte	Mean \pm SD	Upper limit of reference
Zinc protoporphyrin IX	0.64 \pm 0.22 $\mu\text{mol}/\text{l}$	<1.2 $\mu\text{mol}/\text{l}$
Protoporphyrin IX	<0.2 $\mu\text{mol}/\text{l}$	<0.2 $\mu\text{mol}/\text{l}$

^a E.I. Minder, unpublished results from at least 20 healthy volunteers.

31.6 Pathological Values/Differential Diagnosis

■ Differential Diagnosis in Acute Porphyrrias During Attacks

Disease	ALA/PBG in 24 h urine	Fecal coproporphyrins	Fecal coproporphyrin isomer ratio (I/III)	Fecal protoporphyrin	PBG-deaminase	Plasma emission spectrum (626 nm)
31.2 AIP	>5 times upper normal	n-(↑)	>1.0	n	↓-n	n
31.5 HC	>5 times upper normal	↑	<1.0	n	n	n
31.6 PV	>5 times upper normal	↑	<1.0	↑	n	+

■ Differential Diagnosis of δ -Aminolevulinic Acid Deficiency

Disease	Urinary ALA	Urinary PBG	Urinary uroporphyrin	Urinary coproporphyrins	ALA-dehydratase	Peripheral red blood cells	Further analyses
31.1 ALA-D	>5 times upper normal	Normal	Normal	↑ (Coproporphyrin III)	↓	Normal	Lead concentration in blood normal
Lead intoxication	Increased	Normal	Normal	↑ (Coproporphyrin III)	↓	Hypochromic anemia, basophile punctation	Lead concentration in blood increased
Tyrosinemia I ^a	Increased	Normal	Normal	↑ (Coproporphyrin III)	↓	Normal	Blood tyrosin ↑

^a Diagnosis s. Chap. 4.

■ Differential Diagnosis in Cutaneous Porphyrias with Skin Blisters and Skin Fragility

Disease	Urinary porphyrin precursors	Urinary porphyrins	Fecal porphyrin	Remarks
31.3 CEP	n	All urinary porphyrin I-isomers ↑	All fecal porphyrin I-isomers ↑	Uro-cosynthase activity low
31.4 PCT	n	Uroporphyrin ↑; heptacarboxy- ↑ (about 50–70% of uro-), hexacarboxy- ↑, pentacarboxyporphyrin ↑, often coproporphyrin I > III	Uroporphyrin ±; heptacarboxy- ↑, hexacarboxy- ↑, pentacarboxyporphyrin ↑, isocoproporphyrin ↑	
31.5 HC	n-↑	Uroporphyrin ±; heptacarboxy- ± (about 30% of uro-), hexacarboxy- ± pentacarboxyporphyrin ±, coproporphyrin III >> I	Coproporphyrin III >> I, both ↑.	s. acute porphyrias
31.6 PV	n-↑	Uroporphyrin ±; heptacarboxy- ± (about 30% of uro-), hexacarboxy- ± pentacarboxyporphyrin ±, coproporphyrin III >> I	Coproporphyrin III → I, both ↑, protoporphyrin ↑	s. acute porphyrias
31.8 HEP	n	Uroporphyrin ↑; heptacarboxy- ↑ (about 70% of uro-), hexacarboxy- ↑, pentacarboxyporphyrin ↑, coproporphyrin I + III ↑	Uroporphyrin ±; heptacarboxy- ↑, hexacarboxy- ↑, pentacarboxyporphyrin ↑, isocoproporphyrin ↑	
31.9 Variants	n-↑	Increased, pattern variable		Enzyme and/or DNA-analysis necessary for diagnosis

■ Differential Diagnosis in Cutaneous Porphyrrias with Acute Photodermatoses

Disease	Erythrocytic porphyrins	Urinary porphyrins	Fecal porphyrin	Remarks
31.7 EPP	Free protoporphyrin ↑ (>6 μmol/l RBC)	Uroporphyrin ±; heptacarboxy- ± (about 70% of uro-), hexacarboxy- ± pentacarboxyporphyrin ±, coproporphyrin I > III	Protoporphyrin ±	Urinary porphyrins increased only if liver disease due to accumulated protoporphyrin is present
31.3 CEP	Uro- ↑, Coproporphyrins ↑	All urinary porphyrin I-isomers ↑	All fecal porphyrin I-Isomers ↑	Acute photodermatosis less often observed than skin blisters (s. 31.6.3)
“sun allergy” (photosensitivity of other causes)	Zinc protoporphyrin ±, free protoporphyrin n	n	n	Increase of zinc protoporphyrin seen in iron deficiency and lead intoxication

31.7 Loading Tests

Loading tests in acute porphyrias (with barbiturates) are discouraged because of possible severe exacerbations, and as diagnosis is based on other means. The cutaneous porphyrias always show significant elevation of porphyrin intermediates with a typical pattern, if a patient is symptomatic and no loading tests for diagnosis are required.

31.8 Diagnostic Flow Chart

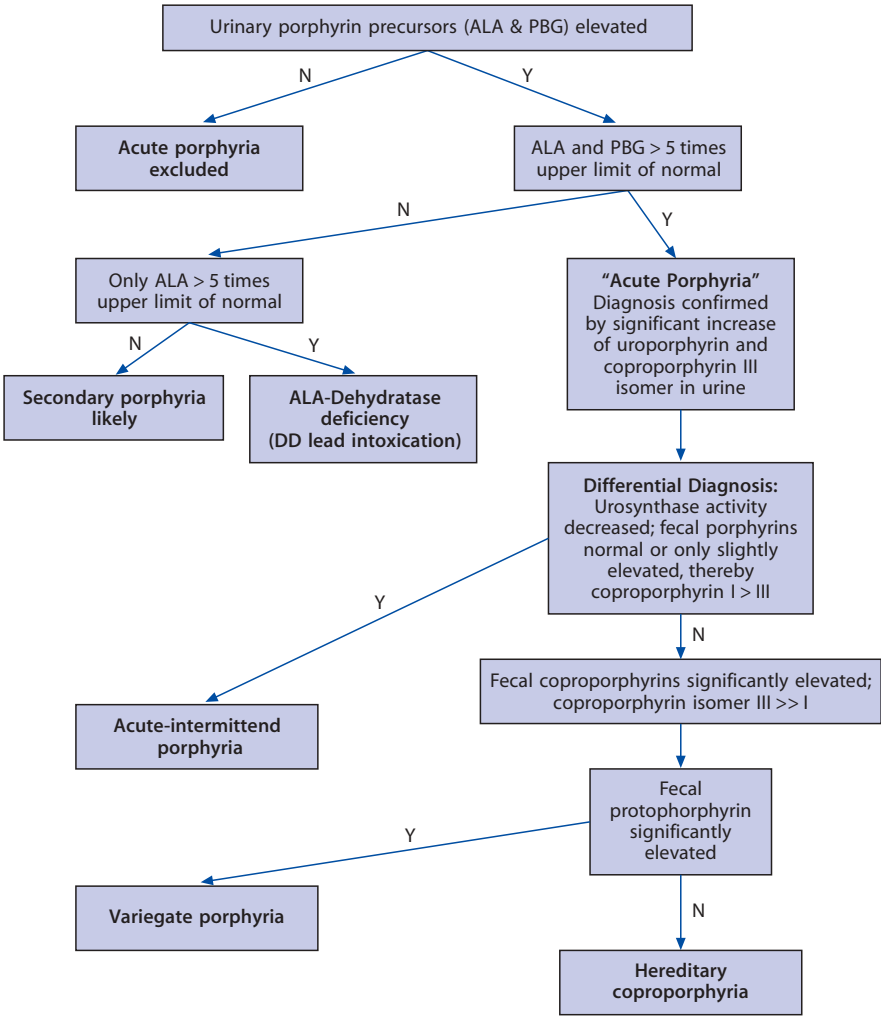


Fig. 31.2. Leading symptom: acute abdominal pain (present at the time of examination)

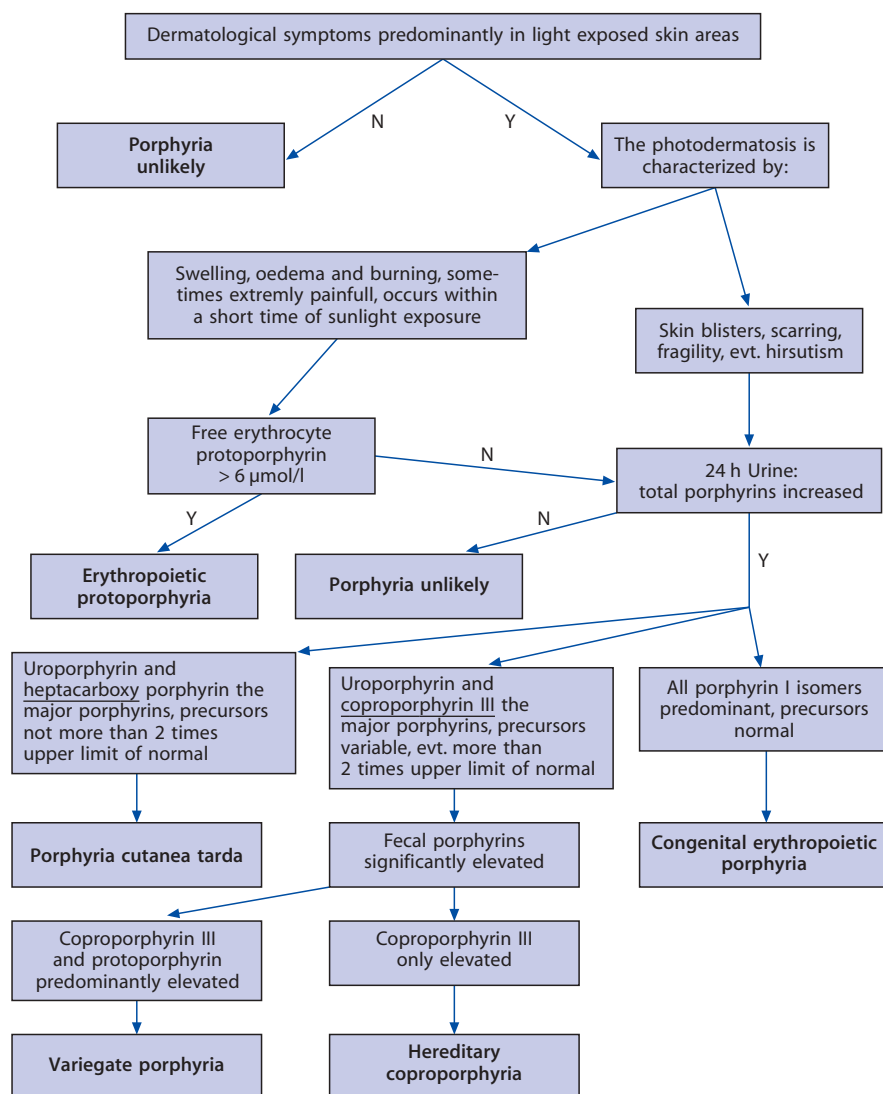


Fig. 31.3. Leading symptom: photosensitivity

31.9 Specimen Collection

Test	Material	Handling	Remarks
First-line diagnostic tests			
Porphyrins (U)	24 hour urine collection	Cool and protected from light	Some laboratories request additions of stabilizers
Porphyrin precursors (U)	24 hour urine collection	Cool and protected from light	Some laboratories request additions of stabilizers
Protoporphyrins (RBC)	Heparinized blood	Cool (but not frozen) and protected from light	
Porphyrins (feces)	3–5 g fresh feces without additions	Cool, evt. frozen, and light protected	
Second-line diagnostic tests			
Enzymes (RBC) ^a	Heparinized blood	Cool, not frozen. Sample should be within 24 hours in the lab	
Enzymes (mononuclear cells) ^b	ACD-blood, EDTA blood	Cool, not frozen. Send sample as fast as possible (<24 h)	Optimal if directly drawn by the lab, that isolates mononuclear cells and sends them frozen at -70°C
DNA-based assays			
Genomic DNA	EDTA blood	Cool	Specified by the lab, dependent on the method used, the preexistent information etc.
cDNA (RT-PCR)	ACD-blood, EDTA blood	Cool, not frozen. Send sample as fast as possible (<24 h)	

^a ALA-dehydratase, urosynthase (syn.: PBG-deaminase, hydroxymethylbilane synthase or pre-uroporphyrinogen synthase), uro-cosynthase or uro-decarboxylase.

^b Coprooxidase, protooxidase or ferrochelatase.

31.10 Prenatal Diagnosis

Prenatal diagnosis is not indicated in the more frequent autosomal dominant porphyrias. In the rare, recessive forms, it is optimal to identify first the family specific mutation(s), as they are mostly “private” ones.

Disorder	Material	Timing	Remarks: contact the lab before sample collection or better before gravidity
31.1 ALA-D	CV	I	No published references
31.3 CEP	CV	I	Residual enzyme activity, or DNA-mutations
31.8 HEP	CV	I	No published reference
31.9 Variant porphyrias	CV	I	No published reference

31.11 DNA Analysis

Mutations of the porphyrias are very heterogeneous and in most cases family specific. DNA analysis is especially useful in family screening in the acute porphyrias, if the mutation has been identified in the index patient. In CEP (31.3) and in EPP (31.7) a phenotype-genotype correlation has been established.

Disorder	Material
31.1 ALA-D deficiency	EDTA-blood
31.2 AIP	EDTA-blood
31.3 CEP	EDTA-blood
31.4 PCT/31.8 HEP	EDTA-blood
31.5 HC	EDTA-blood
31.6 PV	EDTA-blood
31.7 EPP	EDTA-blood
31.9 Variant porphyrias	EDTA-blood

31.12 Initial Treatment (Management while Awaiting Results)

Suspected acute porphyrias: Elimination of any potentially noxious drug, replacement by safe alternatives, if necessary. Oral or parenteral high dose carbohydrate (200–500 g/day). In case of deterioration of neuromuscular functions in combination with a high suspicion of an acute porphyria start with either heme arginate or panhematin (3–4 mg/kg per day times 4–5 days).

In neonates suspected to have any congenital form of porphyria (red urine with pink fluorescence under long UV light) avoid phototherapy for hyperbilirubinemia!

31.13 Summary/Comments

Porphyrias are inborn errors of heme biosynthesis. The more frequent forms are autosomal dominant with incomplete penetrance, the rare forms are autosomal recessive. The dominant forms induce symptoms after puberty, and additional exogenous or endogenous factors influence manifestation. The recessive forms are often symptomatic from birth or even before, but late onset cases with the first disease manifestation in adolescents or in adults are well known.

The porphyrias are characterized by two leading symptoms, severe, colicky abdominal pain (acute porphyrias) and/or photosensitivity mostly as skin blisters (cutaneous porphyrias). Diagnosis in symptomatic periods is

achieved by assessment of urinary porphyrins and porphyrin precursors in a 24 hour urine sample with one exception: erythropoietic protoporphyria. This one is clinically characterized by an acute painful photodermatitis mainly without blisters and the pathognomonic finding is a free (i.e. not zinc chelated) protoporphyrin in the erythrocytes of $>6 \mu\text{mol/l}$.

The cDNA of all enzymes of heme biosynthesis have been characterized and mutations responsible for any of the porphyrias have been described. They are in the overwhelming majority heterogeneous and often family specific. But in some countries, founder effects of either AIP or PV have been elucidated. Phenotype-genotype correlations have been recognized in CEP and EPP. In the last, this will be of relevance to future patient management, as a patient with a missense mutation exhibits a decreased risk to develop the life-threatening complication of terminal liver failure as a patient with a “null allele” mutation.

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