Heme Synthesis Defects and Porphyrias

33

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Summary

Porphyrias are metabolic disorders of the heme biosynthesis. Clinically, they can be differentiated into acute and non-acute porphyrias. The symptomatic phase of acute hepatic porphyrias is characterized by overproduction of neurotoxic porphyrin precursors and porphyrins. Acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and Doss porphyria (ALADP) belong to this group of metabolic disorders. The clinical presentation of the acute hepatic porphyria syndrome includes abdominal, psychiatric, neurological, and cardiovascular symptoms. The diagnosis is based on an at least tenfold increased urinary excretion of porphobilinogen (apart from Doss porphyria and lead intoxication). Besides symptomatic therapy with non-porphyrinogenic drugs, electrolyte correction, and intensive monitoring, intravenous administration of glucose and heme arginate is established for treatment. Among the non-acute types like porphyria cutanea tarda, erythropoietic protoporphyria, and congenital erythropoietic porphyria, the accumulated porphyrins cause photosensitivity of the skin and in some cases severe liver damage. X-linked protoporphyria (XLPP) represents a new type of protoporphyria, with 5-aminolevulinic acid synthase 2 gain of function leading to high concentrations of free protoporphyrin IX. The location of the deficient enzyme within the heme biosynthetic pathway determines the pattern of the accumulated porphyrins. The cDNA of all enzymes of heme biosynthesis have been characterized, and mutations responsible for any of the porphyrias have been described. Besides light protection, there are different therapies depending on the type of non-acute porphyria. Ultimately, liver transplantation may be considered in therapy-resistant cases of acute hepatic porphyrias and bone marrow transplantation in severe cases of erythropoietic porphyrias.

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33.1 Introduction

Porphyrias are a heterogeneous group of metabolic disorders, which are based on genetic deficiencies along the heme synthesis (Bonkovsky et al. 2013; Puy et al. 2010) (Fig. 33.1).

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Clinically it can be differentiated between acute and non-acute porphyrias, pathogenetically between hepatic and erythropoietic porphyrias. Apart from the recessive congenital erythropoietic porphyria (Morbus Günther) and the two types of protoporphyria (EPP,XLPP) all other porphyrias are classified as hepatic.

The clinical presentation of acute hepatic porphyrias includes an abdominal – neuropsychiatric – cardiovascular syndrome, whereas chronic hepatic and erythropoietic porphyrias present with dermatological symptoms due to photodermatosis (Stölzel et al. 1987; Stölzel and Doss 2009).

The symptomatic phase of acute hepatic porphyria is characterized by excessive accumulation and excretion of the porphyrin precursors 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) as well as porphyrins (Bonkovsky et al. 2013; Puy et al. 2010).

Acute porphyrias are biochemically distinguished according to the localization of the affected enzyme. Among acute porphyrias, the acute intermittent porphyria (AIP) is the most common, followed by the variegate porphyria (VP), the hereditary coproporphyria (HCP), and a rare recessive acute hepatic porphyria with 5-aminolevulinic acid-dehydratase deficiency (ALADP, synonym: porphobilinogen synthase defect porphyria, Doss porphyria), which is biochemically very similar to lead poisoning (Doss et al. 1979). Therefore, lead poisoning as toxic and toxo-genetic acute porphyria can be included into the acute types of porphyrias.

In contrast to the acute type, chronic porphyrias such as porphyria cutanea tarda (PCT) as a chronic hepatic porphyria (CHP) and the erythropoietic porphyria (EPP) display characteristics of chronic diseases (Stölzel and Doss 2009).

The diagnosis of clinical symptomatic porphyrias is based on the biochemical analysis, in which each porphyria expresses its own specific diagnostic (excretory) pattern.

Porphyrias are characterized by a huge molecular genetic heterogeneity. They can be caused by a multitude of different mutations. Genetic analysis of clinically "homozygous" porphyrias show that there is quite often a compound heterozygosity. Rare homozygous forms can also be found among dominant autosomal hereditary porphyrias. DNA analysis can be helpful to screen asymptomatic carriers. However, since asymptomatic gene carriers of porphyric disorder are common in the normal population, genetic testing is not recommended for diagnosing acute porphyrias. Recently, modifying genes have been identified that contribute to clinically overt disease and moreover disease severity. In addition there is a considerable interaction between gene defect and environmental factors.

Dual porphyrias were diagnosed in rare cases with clinical and biochemical findings of two porphyrias. For example, coexistent AIP and PCT in the same individual was described.

Apart from the genetic predisposed erythropoietic and hepatic porphyrias, clinical asymptomatic secondary porphyrinurias and porphyrinemias can be detected among a number of different diseases and dysfunctions.

33.2 Nomenclature

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
33.1	X-linked sideroblastic anemia	Erythroid 5-aminolevulinate synthase deficiency	XLSA	*ALAS2*	Xp11.21	5-aminolevulinate synthase 2	300751	All forms
33.2	X-linked protoporphyria	Erythroid 5-aminolevulinate synthase gain of function	XLPP	*ALAS2*	Xp11.21	5-aminolevulinate synthase 2	300752	All forms
33.3	5-aminolevulinate dehydratase porphyria	Doss porphyria	ALADP	*ALAD*	9q34	Delta-aminolevulinate dehydratase	125270	Autosomal recessive
33.4	Acute intermittent porphyria	Porphobilinogen deaminase deficiency	AIP	*HMBS*	11q23-11qter	Porphobilinogen deaminase	176000	Autosomal dominant
33.5	Congenital erythropoietic porphyria	Uroporphyrinogen III synthase deficiency Morbus Günther	CEP	*UROS*	10q25.2-26.3	Uroporphyrinogen III synthase	263700	Classic form

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
33.6	Porphyria cutanea tarda types I, II, and III and hepatoerythropoietic porphyria	Hepatic uroporphyrinogen decarboxylase deficiency chronic hepatic porphyria	PCT/HEP	*UROD*	1p34	Uroporphyrinogen decarboxylase	176100	All forms
33.7	Hereditary coproporphyria	Coproporphyrinogen oxidase deficiency	HC	*CPOX*	3q12	Coproporphyrinogen oxidase	121300	Autosomal dominant
33.8	Porphyria variegata	Protoporphyrinogen oxidase deficiency	PV	*PPOX*	1q22-q23	Protoporphyrinogen oxidase	176200	Autosomal dominant
33.9	Erythropoietic protoporphyria	Ferrochelatase deficiency	EPP	*FECH*	18q21.3	Ferrochelatase	177000	Autosomal dominant

33.3 Metabolic Pathways

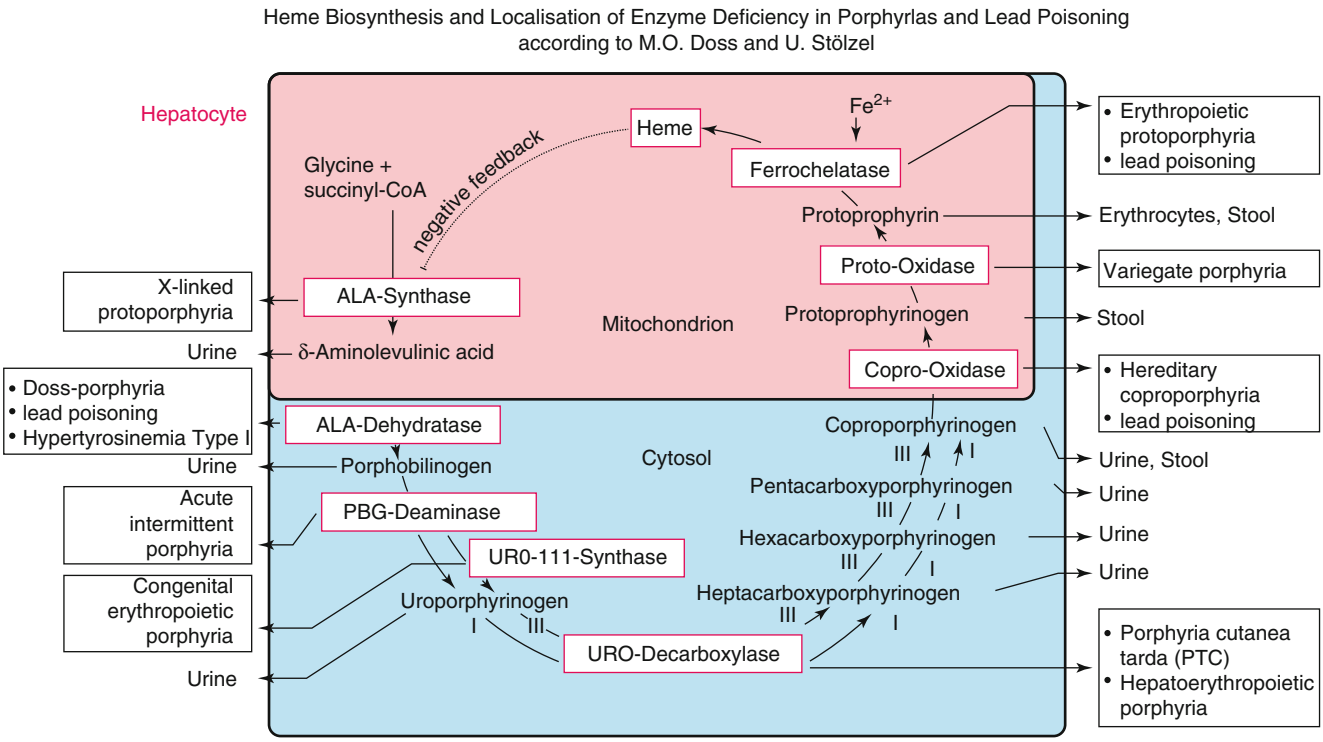

Fig. 33.1 The enzymes of the heme biosynthesis, their subcellular localizations, and associated diseases. There are two differently regulated isoforms of 5-aminolevulinic acid synthase (ALA synthase). ALAS-1 is a ubiquitous enzyme. ALAS-2 is an erythroid-specific enzyme. X-linked protoporphyria is caused by ALAS-2 gain of function mutations

33.4 Signs and Symptoms

Overview on symptomatology

Disorder	Leading clinical symptoms	Onset of symptoms	Frequency
33.1 X-linked sideroblastic anemia	Anemia		
33.2 X-linked protoporphyria	Photosensitivity/liver disease/anemia	Childhood	Rare
33.3 ALA dehydratase deficiency	Abdominal and neurological symptoms	Childhood	Very rare
Lead intoxication	Abdominal and neurological symptoms/ anemia/lead blue line (Burton´s line)	Childhood/ adolescence	Rare
2.1 Hypertyrosinemia type 1[a]	Abdominal and neurological symptoms	Early childhood	Rare
33.4 Acute intermittent porphyria	Abdominal and neurological symptoms/ hyponatremia	After puberty (female > male)	5–10: 100,000
33.5 Congenital erythropoietic porphyria	Photosensitivity: blisters, erosions, mutilations/ anemia/hemolysis/ hepatosplenomegaly/ erythrodontia	Neonatal/childhood	Very rare
33.6 Porphyria cutanea tarda and hepatoerythropoietic porphyria	Liver disease/skin fragility/ photosensitivity/ hypertrichosis	Late adolescence and childhood, respectively	20–50: 100,000
33.7 Hereditary coproporphyria	Abdominal and neurological symptoms, photosensitivity	After puberty (female > male)	0.5: 100,000
33.8 Porphyria variegata	Abdominal and neurological symptoms, photosensitivity	After puberty (female > male)	1: 100,000
33.9 Erythropoietic protoporphyria	Photosensitivity, some patients develop liver disease	Infancy/childhood	0.5: 100,000

[a]The hypertyrosinemia type 1 is not described in detail in this chapter, but the reader is referred to Chap. 2

Enzyme defects along the heme biosynthesis in porphyrias, regulated induction of ALAS1, and major clinical manifestation

Disorder in heme synthesis	Enzyme	Induction of ALAS1	Major Clinical Manifestation			
			Neurovisceral	Cutaneous	Anemia	Liver
X-linked sideroblastic anemia (**33.1**)	ALAS2	–			++	
XLPP (**33.2**)	ALAS2	–	–	++	+	–/+
ALADP (Doss) (**33.3**)	ALAD	+	++	–	–/+	–
Lead intoxication	ALAD	+	+	–	+[a]	+[b]
Hypertyrosinemia type 1[c] (**2.1**)	ALAD	+	+			
AIP (**33.4**)	PBGD	+	++	–	–	–
CEP (Günther) (**33.5**)	UROS	–	–	++	++	–/+
PCT/HEP (**33.6**)	UROD	–	–	+	–	
HCP (**33.7**)	CPO	+	+	–/+	–	+
VP (**33.8**)	PPO	+	+	–/+	–	–
EPP (**33.9**)	FECH	–	–	+	–/+	–/+

[a]Lead inhibits also the enzymes CPO and FECH
[b]"Lead hepatitis"
[c]Hypertyrosinemia is not described in detail in this chapter, but the reader is referred to Chap. 2

Table 33.1 X-linked sideroblastic anemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Hematological	**Anemia**, **microcytic**, **hypochromic**			+	+	+
	Dimorphism (RBC)				+	+
	Sideroblasts (**BM**)			↑	↑	↑
Routine laboratory	**Ferritin** (**S**)			↑	↑	↑
	Transferrin saturation				↑	↑
Special laboratory	5-ALA synthase 2 (RBC)			↓	↓	↓
	Protoporphyrin-Zn (RBC)			↓	↓	↓

Table 33.2 X-linked protoporphyria (XLPP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Dermatological	Burning sensation after sun exposure			+	+	+
	Photosensitivity			++	++	++
Special laboratory	5-ALA synthase 2 (RBC)			↑	↑	↑
	5-aminolevulinic acid (U)			n	n	n
	Porphyrins, all (U)	n	n	n[a]	n[a]	n[a]
	Protoporphyrin feces (or stool)				±	±
	Protoporphyrin IX (**RBC**)			↑↑↑	↑↑↑	↑↑↑
	Protoporphyrin IX-Zn (**RBC**)			↑↑	↑↑	↑↑

[a]In case of extensive and prolonged hepatic exposure to protoporphyrin, there might be increases of coproporphyrin and also the higher carboxylated porphyrin fractions, such as uro- and heptacarboxyporphyrin in urine

Table 33.3 5-aminolevulinate dehydratase deficiency (Doss porphyria)

System	Symptom	Neonatal[a]	Infancy[a]	Childhood	Adolescence	Adulthood
Cardiovascular	Tachycardia			+	+	+
CNS	Coma			+	+	+
	Hyperesthesia			+	+	+
	Motor neuropathy			+	+	+
	Seizures			+	+	+
Digestive	Abdominal pain			+	+	+
	Constipation			+	+	+
	Nausea			+	+	+
	Vomiting			+	+	+
Musculoskeletal	Muscle pain			+	+	+
Renal	Hypertension			+	+	+
Routine laboratory	Color red-brown w. pink fluorescence (U)			+	+	+
	Sodium (P)			↓-n	↓-n	↓-n
Special laboratory	Coproporphyrin III (U)			↑	↑↑↑	↑↑↑
	5-ALA (U)			↑↑	↑↑↑	↑↑↑
	5-ALA dehydratase (RBC)			↓↓↓	↓↓↓	↓↓↓
	PBG (U)			n-↑	n-↑	n-↑

ALADP deficiency, see also Chap. 2 tyrosinemia type 1 (**2.1**) and lead poisoning
[a]No data available

Table 33.4 Acute intermittent porphyria (AIP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Tachycardia				+	+
CNS	Coma				±	±
	Hyperesthesia				±	±
	Motor neuropathy				±	±
	Seizures				±	±
Digestive	Abdominal pain				+	+
	Constipation				±	±
	Nausea				±	±
	Vomiting				±	±
Musculoskeletal	Muscle pain				+	+
Renal	Hypertension				+	+
Routine laboratory	Color red-brown w. red fluorescence (U)				+	+
	Magnesium (P)				↓-n	↓-n
	Sodium (P)				↓-n	↓-n
Special laboratory	5-ALA (U)				↑↑↑	↑↑↑
	PBG (U)				↑↑↑	↑↑↑
	Porphyrins, all (U)				↑↑↑	↑↑↑

Table 33.5 Congenital erythropoietic porphyria (Guenther disease, CEP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Dermatological	Skin blisters	±	+	+	+	+
	Skin fragility	±	+	+	+	+
	Skin scarring and mutilation	n	+	+	+	+
Hematological	Anemia, microcytic, hypochromic, hemolytic	±	+	+	+	+
Routine laboratory	Color red-brown w. red fluorescence (U)	+	+	+	+	+
Special laboratory	Porphyrins type I isomers (P,U)	↑↑	↑↑	↑↑	↑↑	↑↑
	Porphyrins, all (P,U)	↑	↑↑	↑↑	↑↑	↑↑

Table 33.6 Porphyria cutanea tarda types I, II, and III and hepatoerythropoietic porphyria (PCT, HEP)

System	Symptom	Neonatal	Infancy	Childhood (HEP)	Adolescence	Adulthood
Dermatological	Skin blisters, Skin fragility			+	±	+
	Hypertrichosis			+	±	+
Digestive	Elevated liver enzymes (ALT > AST, γ-GT), Ferritin (S)			+	±	±
Routine laboratory	Color red-brown w. red fluorescence (U)			+	±	+
Special laboratory	5-ALA/PBG (U)			n	n	n
	Porphyrins, all (P,U)			↑↑↑	↑	↑↑↑
	Porphyrins, uro- and heptacarboxy > copro (P, U)			↑↑↑	↑	↑↑↑
	Isocoproporphyrin (F)			↑	n-↑	n-↑

Table 33.7 Hereditary coproporphyria (HCP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescense	Adulthood
Cardiovascular	Tachycardia				+	+
CNS	Coma				±	±
	Hyperesthesia				±	±
	Motor neuropathy				±	±
	Seizures				±	±
Dermatological	Blisters				±	±
Digestive	Abdominal pain				+	+
	Constipation				±	±
	Nausea				±	±
	Vomiting				±	±
Musculoskeletal	Muscle pain				+	+
Renal	Hypertension				+	+
Routine laboratory	Color red-brown w. red fluorescence (U)				+	+
	Magnesium (P), Sodium (P)				n-↓	n-↓
Special laboratory	5-ALA (U)				↑↑	↑↑
	PBG (U)				↑↑	↑↑
	Porphyrins, all (U)				↑↑↑	↑↑↑
	Coproporphyrin III (F)				↑↑↑	↑↑↑

Table 33.8 Porphyria variegata (VP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Tachycardia				+	+
CNS	Coma				±	±
	Hyperesthesia				±	±
	Motor neuropathy				±	±
	Seizures				±	±
Dermatological	Blisters				±	±
Digestive	Abdominal pain				+	+
	Constipation				±	±
	Nausea				±	±
	Vomiting				±	±
Musculoskeletal	Muscle pain				+	+
Renal	Hypertension				+	+
Routine laboratory	Color red-brown w. pink fluorescence (U)				+	+
	Magnesium (P)				↓-n	↓-n
	Sodium (P)				↓	↓
Special laboratory	5-ALA (U)				↑↑	↑↑
	PBG (U)				↑↑	↑↑
	Porphyrins, all (U)				↑↑↑	↑↑↑
	Coproporphyrin III and Protoporphyrin IX (F)				↑↑↑	↑↑↑

Table 33.9 Erythropoietic protoporphyria (EPP)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Dermatological	Edema in light-exposed areas		±	+	+	+
	Photosensitivity, acute painful		±	+	+	+
Digestive	Liver dysfunction		n	n-++	n-++	n-++
	Pigment Gallstones			+	+	+
Hematological	Anemia		±	±	±	±
	Microcytosis		±	±	±	±
Routine laboratory	Ferritin (S)		↓-n	↓-n	↓-n	↓-n
	Iron (S)		↓-n	↓-n	↓-n	↓-n
Special laboratory	Free protoporphyrin (RBC)		↑↑	↑↑	↑↑-↑↑↑	↑↑-↑↑↑
	Coproporphyrin (U)		n	n-↑	n-↑↑	n-↑↑

33.5 Reference Values

Urinary excretion of porphyrin precursors and porphyrins

Metabolite	24-h value	Related to creatinine
ALA	<49 µmol	<9.1 µmol/mmol
PBG	<7.5 µmol	<1.4 µmol/mmol
Uroporphyrin	<33 nmol	<6 nmol/mmol
Coproporphyrin I	<51 nmol	<10 nmol/mmol
Coproporphyrin III	<102 nmol	<20 nmol/mmol

Fecal porphyrin excretion

Metabolite	Upper limit of reference
Coproporphyrin I	<26 nmol/g dry weight
Coproporphyrin III	<11 nmol/g dry weight
Protoporphyrin	<80 nmol/g dry weight

Erythrocytic porphyrins

Metabolite	
Zinc protoporphyrin IX	<385 nmol/l
Protoporphyrin IX free	<89 nmol/l

33.6 Pathological Deviations and Values

Biochemical markers in primary and secondary disorders of heme biosynthesis

	33.2	**33.3**		**2.1**	**33.4**	**33.5**	**33.6**	**33.7**	**33.8**	**33.9**
Sample/metabolite	XLPP	ALADP	Lead-intox	HTT1	AIP	CEP	PCT/HEP	HCP	VP	EPP
Urine										
5-ALA	n	↑↑	↑↑	↑-↑↑	↑	n	n	↑	↑	n
PBG	n	n	n-↑	n	↑	n	n	↑	↑	n
5-ALA/PBG	n	↑	↑	↑	↑	n	n	↑	↑	n
Porphyrin I isomers						↑				
Uroporphyrins, total	n-↑	n-↑	n-↑	n	↑	↑↑	↑↑	↓-n	↓-n	n-↑
Uroporphyrins I	–	–			–	↑↑	↑↑	–	–	
Uroporphyrins III					↑	–	↑↑			
Heptacarboxyporphyrin	n-↑	n-↑	n	n	↑		↑	n-↑	n-↑	n-↑
Hexacarboxyporphyrin	n	n-↑	n	n	↑		↑	n-↑	n-↑	n
Pentacarboxyporphyrin	n	n	↑	n-↑	↑		↑	n-↑	n-↑	n
Coproporphyrins, total	n-↑	↑↑	↑↑	↑↑	↑↑	↑↑	n-↑	↑↑	↑↑	n-↑
Coproporphyrin I > III						>1				+
Coproporphyrin III > I		+	+	+				+	+	
Coproporphyrin III			↑↑	↑↑				↑	↑	
Feces										
Porphyrin I isomers						↑				
Uroporphyrins	n	n	n			n	n-↑			n
Heptacarboxyporphyrin	n	n	n			n-↑	↑			n
Hexacarboxyporphyrin	n	n	n			↑	↑			n
Pentacarboxyporphyrin	n	n	n			↑	↑			n
Isocoproporphyrin			–				↑			–
Coproporphyrins	n	n	n-↑		n-↑	↑↑		↑	↑	
Coproporphyrin III > I								+	+	
Coproporphyrin I/III						>1		<1	<1	>1
Protoporphyrin	n-↑	↑			n			n	↑	n-↑↑
Red blood cells										
Uroporphyrin						↑				
Coproporphyrin						↑				
Zinc protoporphyrin	↑↑	↑	↑↑			↑				↑
Protoporphyrin IX, free	↑	↑	↑			↑	n-↑			↑↑
Various										
PBG deaminase					↓-n[a]	n	n	n	n-↓	n
5-ALS-Dehydratase		↓↓	↓-↓↓	↓	n	n	n	n	n	n
Uroporphyrinogen decarboxylase					n	n	n-↓↓	n	n	n
Emission maximum of plasma fluorescence spectrum on excitation with 405 nm (nm)	624–635	615–619	615–618		618–620	615–618	618–620	618–620	624–627	624–635

[a]Normal activity only in case of non-erythroid splice site mutation variant

33.7 Diagnostic Flowcharts

Characteristic clinical presentation of porphyrias

Characteristic clinical presentation (scenario 1–3)*		
 1	 2	 3
Patient after puberty and mostly <40 years old	Patient often >40 years old	Patients in childhood
Abdominal pain, intermittent and colic-like, nausea, vomiting, constipation, and ileus symptoms Tachycardia, hypertension	Easy vulnerability of the skin and blisters on sunlight-exposed skin areas	Burning, itching, pain, edemas, and erythema on sunlight-exposed areas
Dark-reddish urine Hyponatremia	Hypertrichosis close to the temples and to the cheekbone as well as periorbital	Mild anemia with hypochromia and microcytosis
Peripheral motor neuropathy, paresthesias, seizures Psychiatric symptoms, behavioral changes, hallucinations	Associated with 1. Iron overload 2. Hepatitis C 3. Alcohol consumption 4. Estrogens (contraceptives, postmenopausal)	
		
Acute hepatic porphyrias (AIP, HCP,VP, ALADP) and lead intoxication and hypertyrosinemia type 1**	Chronic hepatic porphyria porphyria cutanea tarda and HEP***	Erythropoietic protoporphyria and XLPP****

*Please note: in order to allocate porphyrias, the schema was simplified, and a number of exceptions exists in clinical practice
**Diagnostic tools help to subclassify acute hepatic porphyrias using criteria listed in the Table 33.6
***The diagnosis of a PCT and HEP is based on an excessive increase of uro- and heptacarboxyporphyrin up to a proportion of 80 % of total urinary porphyrin excretion increase. The excretion of PBG remains normal, while urinary ALS can be slightly elevated. The corresponding concentration of plasma uro- and heptacarboxyporphyrin and of stool isocoproporphyrin is increased. Characteristic red porphyrin fluorescence of the liver biopsy, if exposed to long-wave UV light (Woods light, 366 nm)
****In XLPP up to 30 % of total elevated protoporphyrin is zinc bounded

33.8 Specimen Collection

Test	Material	Handling
First-line diagnostic tests:		
Fluorescence scan	1 ml serum, plasma (heparin, EDTA)	Light protected and cool
5-Aminolevulinic acid Porphobilinogen (Porphyrin precursors)	5 ml urine (spot sample or 24 h collection)	Light protected and cool
Porphyrins	5 ml urine (spot sample or 24 h collection, 5 g feces	Light protected and cool
Free protoporphyrin Zinc protoporphyrin	3 ml EDTA blood or heparinized blood	Light protected and cool
Second-line diagnostic tests:		
Enzyme activity tests	5 ml heparinized blood or ACD blood	Cool, not frozen
Molecular genetic assays		
Genomic DNA	EDTA blood or isolated DNA	–
cDNA	EDTA blood	Rapid sample transport (<12 h)

33.9 Treatment

Acute Porphyrias (ALADP; 33.3, AIP; 33.4, HCP; 33.7, VP; 33.8)

General treatment strategies include admitting the patient in to an intensive care unit, analgesic therapy, glucose infusion, correction of electrolyte abnormalities and stopping porphyrinogenic medication (Anderson et al. 2005). The most important therapeutic measures are summarized in the table below.

Therapy of Acute Porphyrias

1. Withdraw unsafe medication and intensive care unit observation
2. Treatment with glucose or together with heme
Intravenous glucose (300–500 g/day) should be given for mild symptoms (moderate pain, no paresis or hyponatremia). Glucose combined with insulin is considered to be more effective than glucose alone
CAVE: Large volumes of 10 % glucose may increase risk for hyponatremia
Severe symptoms and neurological complications should be treated as soon as possible with intravenously given human heme arginate (Normosang®, Orphan Europe) (3 mg/kg body weight for four consecutive days). After infusion, preferably into large vein normal saline should be infused for 15 minutes to reduce local toxicity
We suggested to dilute the human heme arginate in 100 ml of human albumin (4–20 % depending on country availability) instead of normal saline solution to avoid damage of the veins. Heme as a lyophilized powder (Panhematin®; RECORDATI Rare Disease) is available in the United States
3. Monitoring and correction of electrolytes including sodium and magnesium
Analgesic therapy: aspirin, gabapentin, morphine derivatives
In case of tachycardia and hypertension: metoprolol, propranolol, valsartan
In case of unrest and vomiting: lorazepam, phenothiazines, ondansetron
In case of ileus: neostigmine
In case of respiratory failure: mechanical ventilation
In case of infection: penicillin and derivatives, cephalosporins, imipenem, aminoglycosides
In case of paresis: physiotherapy
Monitoring: urinary excretion of ALA, PBG, and porphyrins in AIP and additionally fecal excreted porphyrins in HCP and VP

Glucose and more importantly intravenously applied heme downregulate the metabolic dysregulation (Doss and Verspohl 1981). Mild cases can be treated with glucose alone (Anderson et al. 2005). Neurological symptoms should be immediately treated with heme in order to reverse and avoid progress or persistence. The so-called glucose effect was recently confirmed by elucidating regulatory links between hepatic heme biosynthesis – and glucose metabolism via nuclear receptors including PGC-1α (Handschin et al. 2005). Glucose combined with insulin is considered to be more effective than glucose alone. On one hand, fasting worsens; on the other hand, glucose can help to treat mild clinical manifestations of acute porphyria. If tolerated, diet rich in carbohydrates or oral glucose can be added to or replace intravenous application. Large volumes of 10 % glucose may increase risk for hyponatremia. Intravenously given human heme (3 mg/kg body weight for four consecutive days, Normosang®, Orphan Europe) increases the hepatic heme storage, improves the function of hepatic hemoproteins, represses ALA synthase, and decreases the overproduction and consequently urinary excretion of ALA and PBG within days (Bonkowsky et al. 1971; Bonkovsky 1993).

After infusion, preferably into a large vein to reduce local toxicity, normal saline should be infused for 15 minutes to reduce local toxicity. We suggest to dilute the human heme arginate in 100 ml of human albumin (4–20 % depending on country specific availability) instead of normal saline solution in order to avoid damage of the veins. Heme as a lyophilized powder (Panhematin®; RECORDATI Rare Disease) is available in the United States where human hemin (Normosang®) lacks FDA approval. Prophylactic heme application within periods ranging from weekly to monthly is used to prevent repeated clinical manifestations. Frequent treatment with heme leads to iron overload since 100 mg of heme contains 8 mg iron. Moreover, heme induces the hemoxygenase 1. Recently heme arginate-associated inflammatory reactions such as elevation of interleukin 6 and metabolic stress were observed. Taken together these effects may explain tachyphylaxis with subsequent need to shorten the interval between therapeutic applications (Bonkovsky et al. 2013). Long-term application of heme arginate should be scrutinized critically.

Heme therapy was found to be helpful to relieve symptoms in lead intoxication and ALADP.

Intravenously applied recombinant PBD reduced PBG levels but did not show any benefit on clinical endpoints.

Ultimately, in severe and complicated disease, liver transplantation can cure the disease (Seth et al. 2007). Complete normalization of porphyrin metabolism after liver transplantation proves the fact that acute porphyrias are diseases of the liver. Using adenoviral vectors the hepatic enzymes defects were reversed. So far seven patients have been included, and patients as well as physicians wait for hopefully encouraging short- and long-term results. Transplantation of hepatocytes may be an option for the future. Using small interfering RNA in order to silence hepatic ALAS 1 may be helpful to inhibit ALA und PBG overproduction.

In women with acute porphyria, pregnancy is in general not at risk, although progesterone potently induces liver heme production (Kühnel et al. 2002). However, pregnancy-associated vomiting and subsequent caloric deficiency should be normalized promptly by glucose infusion.

For those women suffering from frequent attacks related to menstrual cycle, gonadotropin-releasing hormone analogues, combined with low-dose estrogen patch to suppress menopausal symptoms, can be helpful. Before treatment with LH-RH- agonist is considered, low-dose hormonal oral contraceptives should be used under strict control of the urinary excretion of porphyrin precursors and porphyrins.

The H2 receptor antagonist cimetidine was successfully used in a few patients. The reports on LH-RH agonists and even on cimetidine are non consistent, and more data from placebo controlled double blinded studies are not available so far. The H2 blocker cimetidine can obviously be used safely on patients with acute porphyria. Parenteral injected

magnesium was reported to be helpful in case of epileptic seizures.

Avoiding porphyrinogenic medication, alcohol and physical stress is of major importance, as well as a balanced diet with a high percentage of carbohydrates. The patients should be advised not to smoke. Patients with acute porphyria should take special care to avoid infections and other diseases, and the porphyrin precursors ALA and PBG should be monitored in order to detect and to effectively treat a renewed porphyria manifestation as soon as possible.

Based on experimental work, pharmacological data, and clinical reports, safe und unsafe drugs are listed (Table 33.10) (Stölzel et al. 2009). International guidelines are useful to individually handle problems (www.drugs-porphyria.org, www.porphyria-europe.com).

Table 33.10 Safe and probably safe drugs in acute hepatic porphyrias

Anesthesia	Allergy, immune system, and respiratory tract	Cancer
(Atropine)	Acetylcysteine	Anakinra
(Bupivacaine)	(Betamethasone)	Asparaginase
(Glycopyrronium)	Cromoglicic acid	Basiliximab
(Isoflurane)	Epinephrine	Bleomycin
(Neostigmine)	Etanercept	Cisplatin
(Pancuronium)	Immunoglobulins	Daclizumab
(Rocuronium)	Infliximab	Filgrastim
Suxamethonium	(Loratadine)	Lenograstim
	Salbutamol	Pegfilgrastim
	(Triamcinolone)	Trastuzumab

Circulation and heart	Coagulation	Diuretics
Adenosine	Abciximab	Amiloride
(Acetylsalicylic acid)	Antithrombin III	(Furosemide)
Atenolol	Dalteparin	(Hydrochlorothiazide)
(Atropine)	Dipyridamole	
Candesartan	Enoxaparin	
Digoxin	Heparin	
Dobutamine	Streptokinase	
Dopamine	Urokinase	
Enalapril	(Warfarin)	
Eprosartan		
Glyceryl trinitrate		
Lisinopril		
Magnesium		
Metoprolol		
Propranolol		
Sotalol		
Valsartan		

Gastrointestinal tract	Hormones	Infection (bacterial)
Cimetidine	Epoetin alfa	Amikacin
Lactulose	Glucagon	Amoxicillin-clavulanate
(Loperamide)	(Goserelin)	(Azithromycin)
(Ondansetron)	Insulin	Benzylpenicillin
Ranitidine	Levothyroxine	(Cefotaxime)

Table 33.10 (continued)

Gastrointestinal tract	Hormones	Infection (bacterial)
Senna	Liothyronine	(Ceftriaxone)
Ursodeoxycholic acid	Oxytocin	(Cefuroxime)
	Tetracosactide	(Ciprofloxacin)
		(Ertapenem)
		Gentamicin
		(Imipenem)
		(Meropenem)
		Methenamine
		(Moxifloxacin)
		Netilmicin
		(Ofloxacin)
		Phenoxymethylpenicillin
		Piperacillin
		Teicoplanin
		Tobramycin
		Vancomycin

Infection (fungal)	Infection (viral)	Metabolism
(Amphotericin)	(Abacavir)	Alendronic acid
(Caspofungin)	Aciclovir	(Bezafibrate)
	(Didanosine)	Colestyramine
	(Famciclovir)	Insulin
	(Foscarnet)	Metformin
	Ganciclovir	(Nicotinic acid)
	(Lamivudine)	Risedronic acid
	(Ribavirin)	
	(Tenofovir)	
	Valaciclovir	
	Valganciclovir	

Neurology	Pain	Psychiatry
(Gabapentin)	Acetylsalicylic acid	Chloral hydrate
Magnesium	Buprenorphine	Chlorpromazine
(Vigabatrin)	(Fentanyl)	Fluoxetine
	Morphine	Fluphenazine
	(Paracetamol)	(Haloperidol)
	Pethidine	Lithium
		(Lorazepam)

Chro Porphyria cutanea trada; Hepatoerythropoietic Porphyria (PCT/HEP; 33.6)

Phlebotomy and treatment with low-dose chloroquine are therapeutically effective in PCT. The therapeutic aim is the elimination of accumulated porphyrins from the liver and other organs. The patients should be advised to avoid known precipitation factors. For patients with advanced liver cirrhosis and reduced albumin synthesis, phlebotomy is contraindicated.

In most cases, the dosage of 125 mg chloroquine twice a week leads to metabolic and clinical remission (Koestler and Wollina 2005). In case of excessive urinary porphyrin excretion of more than 10 mg/day, the treatment can be started with weekly phlebotomy and after 1 month continued with chloroquine for several months up to 1 year.

The treatment can be abandoned when the urinary porphyrin excretion stabilizes in a subclinical level (<0.3 mg/day).

A complete normalization of the porphyrinuria is rare, and in particular, it cannot be expected in case of a genetic disposed form. Since a low to a moderate increased porphyrinuria does not cause clinical symptoms, further treatment is not recommended. Steatosis of liver cells and siderosis can regress after phlebotomy as well as after a therapy with chloroquine (Stölzel et al. 2003). Chronic hepatitis C is associated with PCT (Stölzel et al. 1995). After iron depletion, treatment of chronic hepatitis C should be initiated with combination of protease inhibitor, pegylated, interferon-alpha-2a, and ribavirin (Bonkovsky et al. 2013).

Erythropoietic Protoporphyria (EPP; 33.9)

The light sensitivity is symptomatically treated with beta-carotene with a dosage of 50 up to 200 (300) mg/day. Monitoring of serum carotene levels is recommended (11–15 μmol/L). EPP is characterized by sensitivity to visible light; conventional sunscreens that protect against ultraviolet radiation (particularly UVB) are usually not effective. Reflectant sunscreens based on titanium dioxide or zinc oxide that cover both UVA, UVB, and visible light to a degree will be more effective. Afamelanotide is a new synthetic analogue of naturally occurring alpha-melanocyte-stimulating hormone (α-MSH). After binding to the melanocortin-1 receptor, it induces physiologic melanogenesis independent of the potentially harmful effects of UV light. This leads to increased skin pigmentation and photoprotection. In contrast to acute porphyrias, for patients with EPP, there is in general no restriction for porphyrinogenic substances or medication.

Colestyramine and ursodeoxycholic acid are used for the treatment of EPP-induced liver disease. Colestyramine and other absorbents such as activated charcoal may interrupt the enterohepatic circulation of protoporphyrin. Ursodeoxycholic acid should help to slow the progress of cholestasis and to enhance the biliary elimination of protoporphyrin. Clinical benefit can obviously only be achieved in the early phase of hepatobiliary damage. In order to protect the liver, otherwise damaging agents should be completely avoided. Therefore, vaccination against hepatitis A und B is generally recommended for patients with EPP. Vitamin D substitution is advisible since patients avoid sunlight. Although intravenous heme does not downregulate ALAS 2 in bone marrow, clinical improvement of liver function was described in patients with EPP treated with heme. In some cases, red cell transfusions improved EPP. Plasmapheresis and extracorporeal albumin dialysis (molecular adsorbents recirculation system (MARS), Prometheus) can be used for the elimination of protoporphyrin. Liver transplantation is the therapy of choice in EPP patients with cholestatic liver cirrhosis. Recently for the first time, bone marrow transplantation has been reported in EPP (Wahlin et al. 2007).

Iron supplementation improves protoporphyrin overload, liver damage, and anemia in a new type of X-linked protoporphyria.

Congenital Erythropoietic Porphyria (CEP; 33.5)

Therapeutic measures have been dissatisfactory up to now. Light protection, blood transfusion in case of a severe anemia, and splenectomy can be considered.

Bone marrow transplantation was performed in some cases. Two children were reported to be disease-free for 3 and 2 years posttransplantation. In a mouse model, it has recently been demonstrated to repair mutations of UROS in bone marrow cells with the help of viral vectors. Advance in gene therapy could be a real hope for affected patients in the future.

References

Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, Desnick RJ (2005) Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med 142:439–450

Bonkovsky HL (1993) Advances in understanding and treating 'the little imitator', acute porphyria. Gastroenterology 105:590–594

Bonkovsky HL, Guo JT, Hou W, Li T, Narang T, Thapar M (2013) Porphyrin and heme metabolism and the porphyrias. Compr Physiol 3:365–401

Bonkowsky HL, Tschudy DP, Collins A, Doherty J, Bossenmaier I, Cardinal R, Watson CJ (1971) Repression of the overproduction of porphyrin precursors in acute intermittent porphyria by intravenous infusions of hematin. Proc Natl Acad Sci U S A 68:2725–2729

Doss M, Verspohl F (1981) The "glucose effect" in acute hepatic porphyrias and in experimental porphyria. Klin Wochenschr 59:727–735

Doss M, von Tiepermann R, Schneider J, Schmid H (1979) New type of hepatic porphyria with porphobilinogen synthase defect and intermittent acute clinical manifestation. Klin Wochenschr 57:1123–1127

Handschin C, Lin J, Rhee J, Peyer AK, Chin S, Wu PH, Meyer UA, Spiegelman BM (2005) Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. Cell 122:505–515

Kostler E, Wollina U (2005) Therapy of porphyria cutanea tarda. Expert Opin Pharmacother 6:377–383

Kühnel A, Groß U, Doss MO (2002) Porphyrien. In: Schmailzl KJG, Hachelöer BJ (eds) Schwangerschaft und Krankheit. Blackwell Verlag, Berlin/Wien, pp S440–S453

Puy H, Gouya L, Deybach JC (2010) Porphyrias. Lancet 375: 924–937

Seth AK, Badminton MN, Mirza D, Russell S, Elias E (2007) Liver transplantation for porphyria: who, when, and how? Liver Transpl 13:1219–1227

Stölzel U, Doss M (2009) Porphyrias. In: Dancygier H (ed) Clinical hepatology, principles and practice of hepatobiliary diseases, vol 2. Springer, Berlin, pp 1077–1092

Stölzel U, Doss MO, Dissmann T, Cervós-Navarro J, Riecken EO (1987) Gastroenterologic and neurologic manifestations in acute intermittent porphyria. Med Klin (Munich) 82:520–525

Stölzel U, Köstler E, Koszka C, Stöffler-Meilicke M, Schuppan D, Somasundaram R, Doss MO, Habermehl KO, Riecken EO (1995) Low prevalence of hepatitis C virus infection in porphyria cutanea tarda in Germany. Hepatology 21:1500–1503

Stölzel U, Köstler E, Schuppan D, Richter M, Wollina U, Doss MO, Wittekind C, Tannapfel A (2003) Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. Arch Dermatol 139:309–313

Stölzel U, Brosche C, Koszka C, Stauch T, Teubner A, Doss MO (2009) Safe and probably safe drugs in acute porphyria. Cell Mol Biol 55:147–151

Wahlin S, Aschan J, Björnstedt M, Broomé U, Harper P (2007) Curative bone marrow transplantation in erythropoietic protoporphyria after reversal of severe cholestasis. J Hepatol 46:174–179