

# Porphyrias

**Masao Kondo**

*Tokyo City University, 8-9-18, Todoroki, Setagaya-ku, Tokyo, 158-8586, Japan*

## **Abstract**

Porphyrias are a group of disorders, which induce excess production of porphyrins, as well as cause their accumulation in the tissues. They also increase the excretion of metabolites, as a result of inherited or acquired deficiencies in the activities of the enzymes of the heme biosynthetic pathway. There are 8 types of porphyria. Like other congenital metabolic disorders, this disorder is very rare, has attracted attention for a long time because of its specific symptoms. Porphyria manifests a wide variety of symptoms, including cutaneous, psychoneurotic, gastrointestinal, and endocrine; endogenous and exogenous environmental factors influence the manifestation of these symptoms. Therefore, acute porphyria may be fatal because of false and/or delayed diagnosis. A poor prognosis may be anticipated. Therefore, it is important that we have accurate knowledge of porphyria. This article reviews on the abnormal porphyrin metabolic disorder.

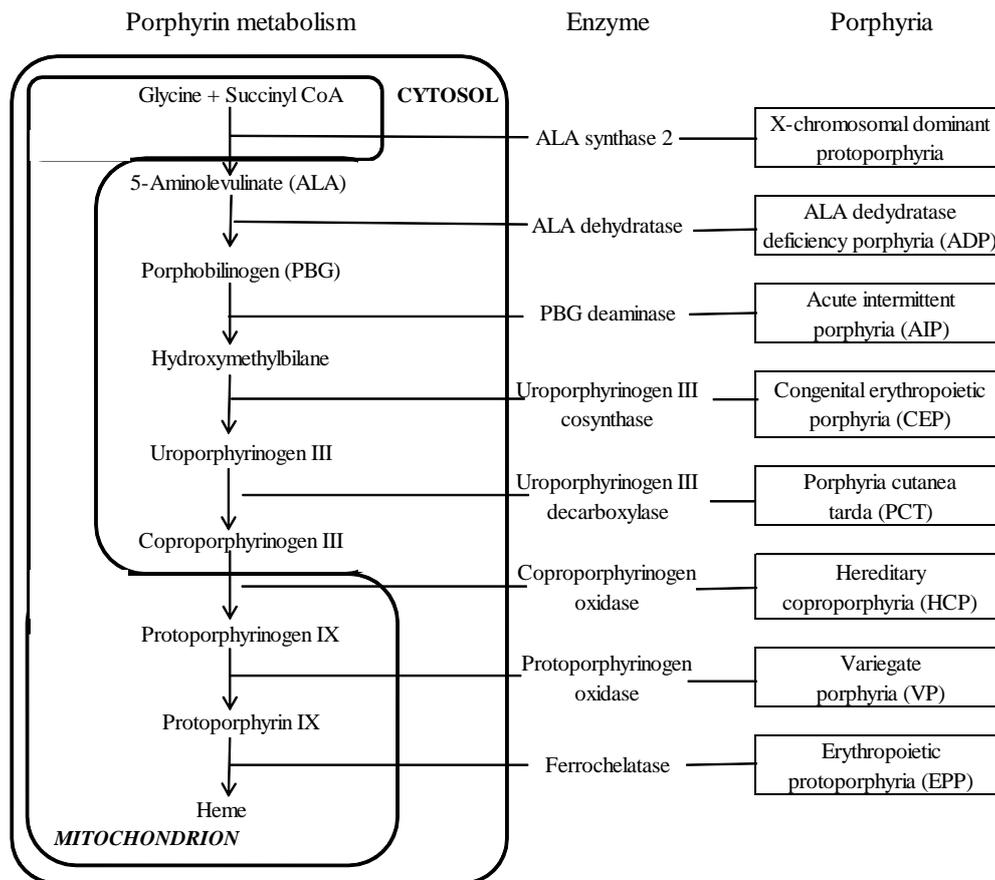
**Key words:** Heme biosynthesis; Acute porphyria; Cutaneous porphyria; Porphyrinuria

## **1. Introduction**

Heme is synthesized by the cooperative activity of eight enzymes localized in intracellular mitochondria and soluble fractions (Fig. 1) [1,2]. It is involved in such processes as detoxification and cellular respiration as a prosthetic group of heme proteins, including hemoglobin and cytochrome P-450. 5-aminolevulinic acid (ALA) synthase (ALAS), the first enzyme in the heme biosynthetic pathway, has two isozymes: erythroid-specific enzyme (ALAS-2 on chromosome X), which is expressed only in erythroid cells, and non-specific enzyme (ALAS-1 on chromosome 3), which is expressed in all organs, including the liver. Regulation of the activities of these isozymes is tissue specific. ALAS-1 is the rate-limiting enzyme in the production of heme in the liver and is controlled via negative-feedback regulation by the intracellular uncommitted heme pool. ALAS-2 is not inhibited by heme [3,4].

The porphyrias are a group of inherited or acquired metabolic disorders resulting from a deficiency in one of the eight enzymes involved in the biosynthesis of heme. Each enzyme deficiency leads to an increased production and accumulation of porphyrin-related metabolites, and leading to excessive excretion of these metabolites in the urine, plasma, or stool [5,6].

**Fig.1 The pathway of heme biosynthesis and enzymatic deficiencies leading to specific types of porphyria.**



## 2. Overview of Porphyrias

### 1) Classification

In 1923, the idea that porphyrias resulted from inborn errors of metabolism was proposed by A. E. Garrod [7]. Since then, eight types of porphyria have been discovered [5,6]. Porphyrias occurring in hepatocytes are classified as hepatic porphyrias, and porphyrias occurring in bone marrow erythroblasts are classified as erythropoietic porphyrias. Clinically, porphyrias that cause mainly neurological symptoms are classified as acute porphyrias, whereas those that cause mainly skin photosensitivity are classified as cutaneous porphyrias (Table 1) [8].

### 2) Differential Diagnosis

Porphyrias are diagnosed by the detection of porphyrin-related metabolites in the urine, blood, plasma, or stool. In some cases, diagnosis requires measurement of enzyme activity and gene studies [9-11].

### 3) Pathological Conditions

Cutaneous porphyrias present with various types of skin symptoms due to phototoxicity

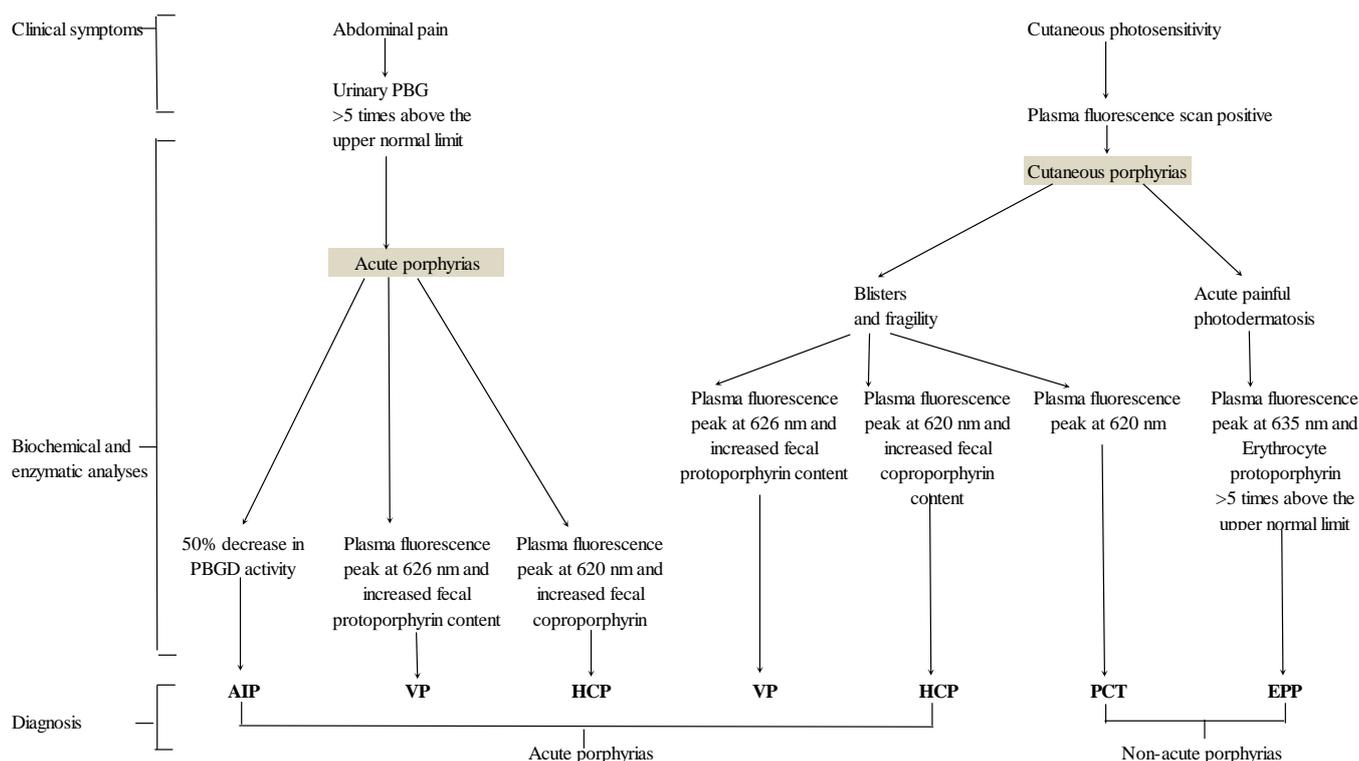
associated with light exposure.

**Table 1. Classification of porphyrias [8]**

Porphyrias		Enzyme defect	Inheritance	Clinical features		Biochemical signs Porphyrins and its precursors	
Classification	Condition			Skin	Neurologic		
Erythropoietic	Cutaneous	Congenital erythropoietic porphyria (CEP)	UROS	Recessive	+++	-	UP I (Urine, Blood)
		Erythropoietic protoporphyria (EPP)	FECH	Dominant	+~++	-	FP (Blood)
		Hepatoerythropoietic porphyria (HEP)	UROD	Recessive	+++	-	UP III (Urine), ZP (Blood)
		Porphyria cutanea tarda (Familial) (f-PCT)	UROD	Dominant	+~+++	-	UP III (Urine), isoCP (Feces)
		Porphyria cutanea tarda (Sporadic) (s-PCT)	UROD	Unknown	+~+++	-	UP III (Urine), isoCP (Feces)
Hepatic	Acute	Variegate porphyria (VP)	PROX	Dominant	+~++	++	ALA, PBG, UP III (Urine), PP, XP (Feces)
		Hereditary coproporphyria (HCP)	CPO	Dominant	-~++	++	ALA, PBG, CP III (Urine), CP (Feces)
		Acute intermittent porphyria (AIP)	PBGD	Dominant	-	++	ALA, PBG (Urine)
		ALAD deficiency porphyria (ADP)	ALAD	Recessive	-	++	ALA (Urine)

Abbreviations used: UP, uroporphyrin; CP, coproporphyrin; ALA, 5-aminolevulinic acid; PBG, porphobilinogen; FP, Free erythrocyte protoporphyrin; ZP, Zinc chelated protoporphyrin; PP, protoporphyrin IX;

**Figure 2. A flowchart illustrates the diagnostic strategy for porphyrias (except for rare homozygous forms). [9]**



Acute porphyrias occur commonly in females between adolescence and middle age; factors such as various kinds of drugs; reproductive events, including menstruation and childbearing; contraceptive pill ingestion; infection; starvation; and stress are invariably involved in triggering the development of the disease. The pathological conditions characteristically present with a broad spectrum of symptoms of the neurologic, gastrointestinal, endocrine, and circulatory systems [12]. Administration of ALA to a patient with abnormal porphyrin metabolism may lead to exacerbations.

#### 4) Treatment

Acute porphyrias are treated by drip infusion of large amounts of glucose. Concurrently, chlorpromazine is given for pain, painful numbness, and insomnia; propranolol for hypertension and tachycardia; and diazepam or chloral hydrate for convulsions. Intravenous administration of hematin or heme arginate has been reported to be effective in improving clinical symptoms and abnormal porphyrin metabolism [13,14]. Cimetidine, which suppresses hepatic ALAS activity, has been reported to be efficacious to such an extent that it corrects abnormal metabolism [15,16].

In cutaneous porphyria, care should be taken to avoid skin injury and exposure to sun light.

#### 5) Incidence

Acute intermittent porphyria (AIP) is common in Northern Europe (most common in Sweden): the estimated incidence per 100,000 inhabitants is 1. Variegate porphyria (VP) is common in Southern African caucasians: the estimated incidence per 1000 inhabitants is 3 [17]. Erythropoietic protoporphyria (EPP) has been reported worldwide, with prevalence between 1:75,000 and 200,000. Although the incidences of porphyrias are somewhat biased, depending on the type, all eight types are distributed worldwide. In Japan, by 2008 a total of 898 cases had been reported since the first case report in 1920 [18].

#### 6) Gene Mutation and Diversity

ALA dehydratase (ALAD) deficiency porphyria (ADP), congenital erythropoietic porphyria (CEP), and hepatoerythropoietic porphyria (HEP) are autosomal recessive disorders. Patients with these porphyrias are clinically and biochemically homozygous, whereas their parents are clinically asymptomatic heterozygotes. In porphyrias, not only the autosomal recessive forms but also the autosomal dominant forms (AIP, EPP, VP, and hereditary coproporphyria (HCP)) do not result from a single mutation; in many cases they result from different mutations, depending on family lines. Such multiple mutations are as diverse as point mutations, additions, and deletions, with large numbers of mutation sites in each. Only rarely have homozygous cases been reported in heterozygous forms of autosomal dominant porphyria.

### **3. Acute Porphyrias**

The acute porphyrias are AIP, VP, HCP, and ADP. When exposed to some environmental factor in addition to drugs or stresses, genetically predisposed people acutely or subacutely manifest multifarious symptoms of the gastrointestinal, neurologic, circulatory, endocrine, and metabolic systems (gene–environment interaction) (Table 2). For acute porphyrias, administration of large amounts of glucose is a common effective treatment. This is

presumably because high doses of glucose suppress the activity of ALAS, the first enzyme in the heme biosynthetic pathway, thereby reducing the production of porphyrin metabolites (the glucose effect) [19,20]. In these acute hepatic porphyrias have increased risks of hepatocellular carcinoma [21,22] and chronic renal failure [23].

**Table 2 Classification of the acute porphyrias highlighting important clinical and epidemiological aspects at a glance. [2]**

Acute porphyrias	incidence	Age of onset	Important aspects
Acute intermittent porphyria	0.5-1 per 100,000	second to fourth decade of life; very rarely before puberty	most common acute porphyria in the world; acute neuro-logical attacks but no photosensitivity/cutaneous symptoms
Variegate Porphyria	approx. 1 per 300 in South Africa ;relatively rare elsewhere	second to third decade of life; usually not before puberty	skin symptoms similar to PCT and acute attacks similar to AIP can occur(neurocutaneous porphyria); founder mutations identified in South Africa and Chile
Hereditary coproporphyrria	very rare (<50 cases reported)	usually not before puberty	acute attacks similar to AIP and cutaneous symptoms including erythema and blistering can occur (neurocutaneous porphyria)
ALAD deficiency porphyria	extremely rare (<10 cases reported)	early and late onset have been described	neurological symptoms similar to AIP can occur; no photosensitivity/cutaneous symptoms

## 1) Acute Intermittent Porphyria (AIP)

### (1) Etiology and Symptoms

AIP is the most prevalent form of acute porphyria. In AIP, decreased porphobilinogen deaminase (PBGD) [hydroxymethylbilane synthase, uroporphyrinogen I synthase] activity and heme levels trigger the de-repression mechanism, leading to excretion of ALA and porphobilinogen (PBG) from the liver in large amounts. Extensive accumulation of ALA and PBG, in the acute phase of AIP, provokes gastrointestinal symptoms such as abdominal pain and vomiting, often accompanied by peripheral neuropathy manifested as numbness and adynamia of the extremities. Although abdominal pain is almost inevitable and severe, objective findings such as tenderness and muscular guarding are seldom observed, so that AIP often mimics ileus or even hysteria. Peripheral neuropathy is almost inevitable, causing such symptoms as adynamia and numbness of the extremities. In addition, central nervous system symptoms such as disturbance of consciousness and convulsion, as well as psychiatric symptoms such as anxiety, depression, delirium, and hallucination, may occur, sometimes leading to misdiagnosis as schizophrenia. In extremely serious cases symptoms of bulbar paralysis may occur; this can be fatal. Circulatory symptoms such as hypertension and tachycardia are also often noted early and clearly reflect the clinical course. In addition, abnormal lipid metabolism, disturbance of carbohydrate metabolism, thyroid dysfunction, ectopic and inappropriate secretion of antidiuretic hormone, and growth hormone abnormalities commonly occur. Most of these symptoms are based on abnormalities of the nervous system, including the autonomic nervous system. No cutaneous symptoms are noted.

## (2) Diagnosis and differentiation

When a female patient between puberty and middle age acutely or subacutely develops abdominal pain or peripheral neuropathy of unknown cause, an acute porphyria should be suspected and urinary ALA and PBG should be measured. The urinary PBG level remains elevated in remission. Healthcare providers should be aware early that AIP mimics acute abdomen and the like (Table 3), causing patients to be subjected to polysurgery. Being a very rare disorder with vague presentation, the diagnosis is often missed by clinicians [8].

**Table 3. Initial diagnosis of acute porphyrias [8]**

Acute abdomen	Liver dysfunction
Ileus	Neuropathy
Appendicitis	Guillain-Barre syndrome
Psychogenic disorders (hysteria)	Ovarian volvulus
Pancreatitis	Ectopic pregnancy
Epilepsy	Gallstone
Hyperemesis gravidarum	Others
Acute peptic ulcer	

## (3) Treatment and prognosis

AIP is treated by administering fluids and glucose in large amounts. Concurrently, individual symptoms are treated by symptomatic therapy. Extreme caution should be taken to ensure proper administration of medications. The prognosis of AIP is excellent as long as early diagnosis is performed and use of contraindicated medications is avoided.

## 2) Variegate Porphyria (VP)

In VP, the levels of all the porphyrins ranging from ALA to protoporphyrin XI (PPXI) are elevated because of a deficiency in PPOX (protoporphyrinogen oxidase). VP presents with medical and neurologic symptoms similar to those of AIP, as well as cutaneous symptoms similar to those of porphyria cutanea tarda (PCT); all of these can develop to different degrees. Acute and cutaneous symptoms are treated in accordance with the treatments for AIP and cutaneous porphyrias, respectively.

## 3) Hereditary Coproporphyrin (HCP)

HCP presents mainly with acute symptoms similar to those of AIP, but HCP symptoms are often milder. HCP symptoms include cutaneous symptoms, which must be differentiated from those of VP. In severe cases (in homozygotes, enzyme activity is only 2% to 10% of normal), harderoporphyrin levels are increased in the urine and feces. In the acute phases, urinary ALA and PBG levels are increased, returning to normal in remission. Fecal crude protein levels are continuously elevated.

## 4) ALAD Deficiency Porphyria (ADP)

ADP is an extremely rare disease: only 7 cases have been reported to date worldwide. ADP is an inherited ALAD deficiency in which mutations of both alleles result in a decrease (to less than a few percent of normal) in hepatic ALAD activity, triggering overproduction of ALA. ADP symptoms, including diverse acute symptoms, are difficult to distinguish from those of AIP.

## 4. Cutaneous Porphyrias

The cutaneous porphyrias are CEP, EPP, HEP, and PCT, all of which present with broad spectra of symptoms of photosensitive dermatosis, as well as liver damage (Table 4).

### 1) Congenital Erythropoietic Porphyria (CEP) (Gunther’s disease [24])

CEP, which presents as the most severe photosensitivity of all the porphyrias, is one of the rarest diseases and is caused by the overproduction of type 1 isomer due to deficiencies in uroporphyrinogen III synthase (UROS). Skin bullae, which develop soon after birth, are severe and are accompanied by ischemia and red urine. In addition to skin lesions, CEP symptoms include finger contracture; nail deformation; defects in the nose, ears, and fingers; hypertrichosis; erythrodontia (exhibiting red fluorescence of the teeth under UV irradiation); splenomegaly; hemolytic anemia; and scleral involvement. Some cases of late-onset CEP have also been reported. No effective therapy for CEP has been established. [25]

**Table 4 Classification of the cutanea porphyrias highlighting important clinical and epidemiological aspects at a glance. [2]**

Cutanea porphyrias	incidence	Age of onset	Important aspects
Porphyria cutanea tarda	most common porphyria worldwide	third to fourth decade of life; usually not before puberty	most frequent type of porphyria worldwide; acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous symptoms include vesicles and bullae, erosions, crusts, milia, scarring, hyperpigmentation, and hypertrichosis; undistinguishable from VP
Erythropoietic protoporphyria	second-highest incidence of the cutaneous porphyrias	early childhood (1-4 years); late onset extremely rare	cutaneous symptoms include erythema, edema, purpura, skin thickening, waxy scars; usually no blistering; in approximately 5% of the cases severe liver disease can occur
Congenital erythropoietic porphyria	very rare (approx. 150 cases reported)	infancy/first decade of life	very severe clinical course; vesicles and bullae, erosions, excoriation, exulceration, crusts, milia, scarring, hyperpigmentation, and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia)
Hepatoerythropoietic porphyria	extremely rare (approx. 25 cases reported)	early infancy	recessive variant of PCT; reported in the USA and Europe; markedly increased photosensitivity and severe clinical course possible; vesicles and bullae, erosions, excoriation, crusts, millia, scarring, and hypertrichosis; mutilation can occur

### 2) Erythropoietic Protoporphyria (EPP)

#### (1) Concept

EPP manifests as skin photosensitivity in infancy, characterized by pain, redness, and swelling immediately after exposure to sunlight. Liver damage is also common in EPP [26].

## (2) Etiology and Symptoms

In EPP, decreased ferrochelatase (FECH) activity produces excessive PPXI in the erythroblasts. PPXI appears in the red blood cells and plasma and is excreted from the liver to the bile and feces, resulting in skin sensitivity, cholelithiasis, and liver damage. Autopsy examination almost always shows hepatic cirrhosis but seldom shows bullae or cicatrization. Symptoms similar to those of angioedema, including stinging (burning), itching, erythema, and swelling, occur at the site of light exposure. Moreover, during the chronic phase, symptoms of skin rash, such as pigmentation, hypertrichosis, and linear scarring due to skin fragility, are commonly noted.

## (3) Diagnosis and Differentiation

In EPP, only PPXI levels in the blood and feces are markedly increased. Detection of fluorescent erythrocytes (even in carriers) and recognition of light hemolysis serve as useful adjuncts to diagnosis. A liver biopsy sample of an EPP patient with concurrent liver damage shows red fluorescence under UV irradiation.

## (4) Treatment and Prognosis

To treat EPP, protection from light is of primary importance. In addition, administration of substances such as  $\beta$ -carotene, cholestyramine resin, cimetidine, hematin, and cholic acid, as well as plasmapheresis, has been attempted, but none has proved to be reliable. EPP patients free of liver damage have a relatively good prognosis.

## 3) Hepatoerythropoietic Porphyria (HEP)

HEP is one of the rarest forms of porphyria in the world and is characterized by abnormal porphyrin metabolism in both the liver and the bone marrow. HEP is considered a homozygous form of familial PCT (fPCT) because of the very low uroporphyrinogen decarboxylase (UROD) activity (7% to 8% of normal). HEP presents with severe photosensitive dermatosis as the main symptom, immediately after birth [27,28].

## 4) Porphyria Cutanea Tarda (PCT)

### (1) Concept

PCT is the most prevalent form of cutaneous porphyria and is characterized by abnormal porphyrin metabolism caused by reduced hepatic UROD activity of the fourth enzyme involved in hepatic heme synthesis, accompanied by photodermatitis and liver damage. Two types of PCT are known: familial PCT (fPCT) and sporadic PCT (sPCT) [29].

### (2) Etiology

Whereas fPCT is associated with mutations in the *UROD* gene, such mutations are not present in sPCT. The mechanism of action underlying sPCT is still unclear. In fPCT, UROD

activity is almost lost because of a deficiency on one allele; thus only the enzyme activity from the normal allele is detected, resulting in a UROD activity of 50% of normal. However, there are many carriers who do not develop fPCT despite having the gene associated with fPCT; this suggests that the development of fPCT involves factors such as excessive intake of alcohol, estrogen, and iron, as may be the case in sPCT [30]. Virus infection, such as hepatitis C and HIV, are also suspected of being contributing factors [31].

### (3) Symptoms and Examination

PCT characteristically presents with cutaneous symptoms such as solar dermatitis and skin fragility, facilitating the formation of bullae and thereby resulting in erosion, cicatrization, and pigmentation. In rare cases, such PCT symptoms are complicated by sclerodermatous changes. Liver damage occurs, with symptoms such as iron deposition, fat changes, necrosis, chronic inflammatory change, deposition of porphyrin-like needle crystals, and fibrosis; these are likely to lead to liver cirrhosis and liver cell carcinoma.

### (4) Diagnosis and Differentiation

fPCT is common in adult females, and sPCT in middle-aged males. Histopathological examination by skin rash biopsy characteristically shows deposition of periodic acid-Schiff (PAS)-positive substances around the blood vessels in the superficial dermis and bulla formation at the dermoepidermal interface, together with deposition of immunoglobulin and complement at the interface. Urine and liver biopsy samples exhibit red fluorescence under UV irradiation. Urinary uroporphyrin (UP) and heptacarboxyl porphyrin (7P) levels are increased [32].

### (5) Treatment and Prevention

In mild cases of PCT, urinary porphyrin levels return to normal only when the causal factors are eliminated. Phlebotomy is performed in patients with markedly high urinary levels of porphyrin. In addition, administration of deferoxamine as an iron chelating agent and of interferon in hepatitis C virus-complicated PCT has been reported to be effective [33,34].

**Table 5. Causes of secondary porphyrinuria**

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• <b>Anemias</b>
Dys erythropoietic, Aplastic, Hemolytic, Pernicious
• <b>Leukemias/lymphomas</b>
AML, CML, ALL, CLL, Hodgkin's disease
• <b>Chemicals and drugs</b>
Barbiturates, benzene, estrogen, ethanol, carbamazepine, carbon tetrachloride, halogenated aromatic hydrocarbons, heavy metal (As, Pb, Hg etc), phenytoin, progestagens
• <b>Hereditary conjugated hyperbilirubinemias</b>
Dubin-Johnson and Rotor's syndromes
• <b>Liver diseases</b>
Alcoholic, cholestatic, chronic hepatitis, chirrhosis, viral hepatitis (especially hepatitis C)
• <b>Miscellaneous causes</b>
Bronze baby syndrome, diabetes mellitus, infectious diseases, myocardial infarction, pregnancy, starvation, etc

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Secondary porphyrinurias are the most common causes of increased porphyrins in the urine. These increases are mild-to-moderate in degree (less than threefold above upper limit of normal), usually mainly due to coproporphyrins. Stool porphyrins are generally normal.  
 Abbreviations used: ALL, acute lymphocytic leukemia; ALM, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; As, arsenic; Hg, mercury; Pb, lead

## 5. Other Aspects of Abnormal Porphyrin Metabolism

It is widely known that abnormal porphyrin metabolism is triggered by many factors, including hepatic disorders, blood disorders, hypermetabolism, and endocrine disorders; poisoning with heavy metals such as lead; halogenated aromatic hydrocarbons such as dioxin and hexachlorobenzene (HCB); and numerous pharmaceuticals, such as phenobarbital, ceftrimide, griseofulvin, and carbamazepine (Table 5) [35] .

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