

Porphyria: Classification and Diagnosis

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Porphyrias are a group of metabolic disorders, at the bottom of which lies a disturbance in the synthesis of the heme; thereby, in most cases, it is about a hereditary enzyme defect. The disease patterns differ depending on the affected enzyme; 1 clinically differentiates between the acute and non-acute forms. In particular, a physician should also be aware of the 2 most common forms of overall rare diseases as an important differential diagnosis. Below is an overview of the clinical manifestations, diagnosis, and treatment options of porphyria.



Definition of Porphyria

Porphyria is a condition characterized by a defective heme synthesis pathway due to enzyme defects, resulting in a clinical syndrome involving the skin, nervous system, and liver at individual levels or cumulatively. Heme production is considered to be a multilevel process controlled by various enzymes.

Locations of Heme Synthesis

The heme is a porphyrin-containing compound that is synthesized in the human body in eight steps. In two-organ systems of the human body, heme synthesis occurs

independently. In the following section, it is described as occurring as heme pools:

- The **erythropoietic heme pool** is formed in the bone marrow and is used in a series of hemoglobin synthesis steps for the erythrocytes.
- The **hepatic heme pool** is formed in the liver and is used for the synthesis of hepatic enzymes that contain a heme. Here, it mainly refers to the cytochrome P450 enzymes.

Localization of the essential expression of the affected enzyme results in the classification of porphyria into **erythropoietic** and **hepatic porphyria**. Hepatic porphyrias are much more common than erythropoietic.

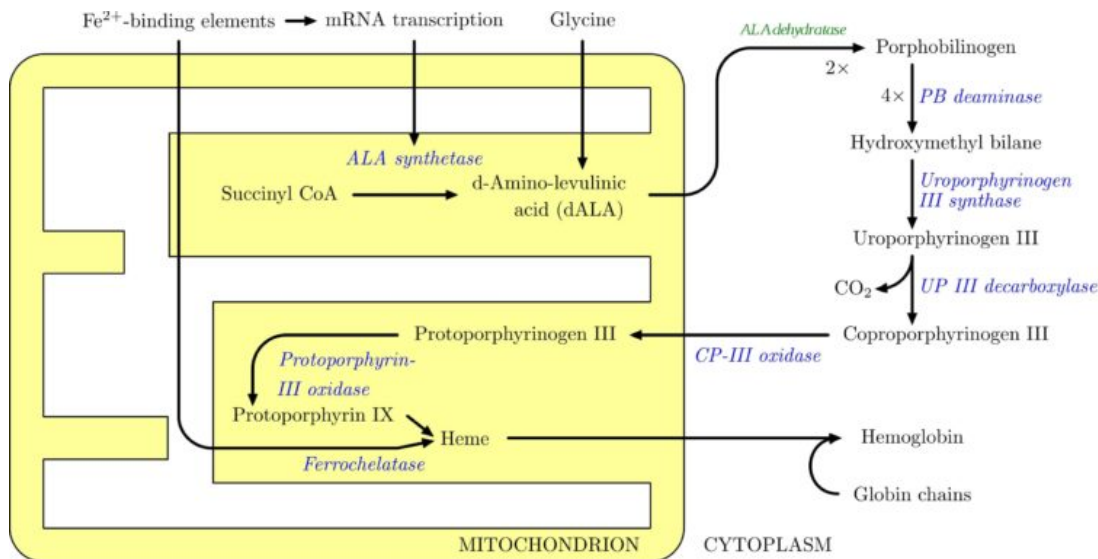


Image: Heme synthesis. By Wmheric. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/).

Pathogenesis of Porphyria

All porphyrias have a similar pathogenesis, in that an enzyme of the biosynthesis of the heme is impaired in its activity by a genetic defect. This impairment results in an accumulation of the substrate of the affected enzyme. These intermediates can cause various kinds of organ damage and symptoms when concentrations are increased. In addition, there is increased excretion through the urine and stool. The allocation of the affected enzyme and type of porphyria following the steps of the heme synthesis are listed here:

Defective enzyme	Form of porphyria
δ -aminolevulinic acid synthase 2	X-chromosomal protoporphyria
δ -aminolevulinic acid dehydratase	Doss porphyria
Porphobilinogen deaminase	Acute intermittent porphyria (AIP)
Uroporphyrinogen 3 synthase	<i>M. Gunther</i>
Uroporphyrinogen decarboxylase	Porphyria cutanea tarda
Coproporphyrinogen oxidase	Hereditary coproporphyria
Protoporphyrinogen oxidase	Porphyria variegata
Ferrochelatase	Erythropoietic protoporphyria

Epidemiology

- The incidence rate of porphyria is almost the same all over the world: 5 cases per 100,000 population. The incidence of symptoms of porphyria in Europe ranges from 130,000 to 510,000 cases per year.
- The estimated risk of porphyria in Europe is 4%.

Classification of Porphyrias

Clinical classification of porphyrias depends upon the pattern of involvement of the organ.

The various types of porphyria are distinguished as follows. Generally, chronic forms show increased skin manifestations, whereas acute porphyria causes more systemic complaints. The most common forms are porphyria *cutanea tarda* (PCT), acute intermittent porphyria (AIP), and erythropoietic protoporphyria (EPP). Other forms, such as Doss porphyria, are extremely uncommon.

1. Erythropoietic porphyria

- Congenital erythropoietic porphyria (also: *M. Gunther*, autosomal recessive)
- Erythropoietic protoporphyria (autosomal dominant)



[Image](#): Photograph showing the presence of lesions and scars on both hands of a patient with congenital porphyria. License: [CC BY 2.0](#).

2. Hepatic porphyria

3. Acute hepatic porphyria

- Acute intermittent porphyria (autosomal dominant)
- Hereditary coproporphyria (autosomal dominant)
- Variegate porphyria (autosomal dominant)
- Doss porphyria (autosomal recessive)

4. Chronic hepatic porphyria

Note: Variegate porphyria is an acute, autosomal dominant, inherited form of porphyria and occurs with a significantly higher prevalence in the White population of South Africa. It is therefore also called **South African genetic porphyria**.

Clinical manifestations vary according to the level of metabolism affected. If enzyme defects are at the initial stage of metabolism, then the neurologic region is mainly affected. If defects occur at the final stages, then cutaneous involvement is present.

Clinical features

Some common signs and symptoms of porphyria are as follows:

- Acute colicky abdominal pain in the left lower abdomen that lasts for hours to days. The pain is rarely accompanied by fever, leukocytosis, or peritonitis. There can be considerable discrepancy between a patient's clinical presentation of pain and objective findings.
- Nausea and vomiting
- Muscular weakness
- Limb pain
- Quadriplegia
- Psychiatric symptoms such as psychosis
- Anxiety
- Skin rash
- Blisters on sun-exposed areas
- Red-brown-colored urine

Diagnosis

- Diagnosis is made on the basis of a typical presentation of signs and symptoms in the absence of other obvious causes and urine examination. After a urine examination, test results can show that excretion of porphobilinogen (PBG) is increased 5-100 times.

Porphyria *cutanea tarda* (PCT)

Etiology and pathogenesis of PCT

The **most common porphyria** is **porphyria *cutanea tarda*** with an incidence of about 15 per 100,000 people. PCT is based on a decrease in the activity of **uroporphyrinogen decarboxylase** (URO-D). In this case, it is a chronic, hepatic porphyria. This progressive form can occur either as **autosomal dominant hereditary** or **acquired**; the peak incidence occurs after 40 years of age. The acquired form results from a deficiency of the enzyme caused by liver damage. The transition of a latent PCT inherited from chromosome 1, in the manifest form, can be triggered by alcohol abuse, estrogens, or infection, and often occurs with hepatitis C.

Note: With 70% of all cases, alcohol is the most common cause of a manifest porphyria *cutanea tarda*.

Symptoms of PCT

The most noticeable symptom of PCT is **photodermatoses**. The skin is extremely light sensitive and responds to exposure with blistering and delayed healing. Scarring often occurs on the face and on the back of the hands of patients who have PCT. Similarly, patients show increased hair growth (**hypertrichosis**) and **hyperpigmentation**. The skin manifestation of PCT can be presumed without a prophylaxis disfiguring extent.



[Image](#): Erosions, crust, and blisters are evident on the hands of this patient with PCT. License: [CC BY 2.5](#).

In addition, the porphyrin deposits cause progressive **liver damage** with pathologically elevated liver function values up to the sonographically detectable nodules. A characteristic symptom is dark-colored urine due to porphyrins. This symptom is referred to as **porphyrinuria**.

Note: The most common localizations of skin damage caused by PCT are on the back of the hand, on the face, and on the neck.

Diagnosis and treatment of PCT

Diagnosis arises on the basis of anamnesis and symptoms, dark-red or brownish discolored urine, proven **porphyrinuria**, and possibly a liver biopsy that can detect metabolites by using fluorescence.

There is no causal treatment. Treatment primarily consists of the avoidance of triggering noxae and consistent avoidance of light exposure. Repeated **bloodletting** can provide recovery through a decreased erythrocyte count.

In addition, medicamentosis can be treated with **chloroquine**, which makes porphyrins complexed and renally excretable. With consistent protection from light exposure with clothing and sunscreen and avoidance of triggering noxae, a good prognosis exists for patients with porphyria *cutanea tarda*, which is determined by the extent of liver damage.

Acute intermittent porphyria (AIP)

Etiology and pathogenesis of AIP

The **second most common form** of porphyria is acute intermittent porphyria (AIP). It is counted as acute hepatic porphyria and has its peak incidence in the third decade of life. It has been shown that only about 10% of the autosomal dominant inherited genetic defects turn into porphyria. On the other hand, about one-quarter of unrelated patients show *de novo* mutations. The affected enzyme is **porphobilinogen deaminase** with increases in the preceding intermediates: porphobilinogen, δ -aminolevulinic acid, and porphyrins. The genetic defect is located at various points of the gene on chromosome 11.

Apart from stress, infections, and hypoglycemia, a variety of medications, in particular, and other porphyrinogenic substances are triggers of an acute manifestation in this form.

These triggers include alcohol, metoclopramide, furosemide, diclofenac, angiotensin-converting enzyme (ACE) inhibitors, statins, and many anesthetics such as barbiturates, among others.

Symptoms of AIP

Acute porphyria syndrome is very diverse in clinical presentation and often results in misdiagnoses. Leading the way are three main symptoms and the frequent association with intake of medication.

Abdominal discomfort with colicky pain and vomiting are key symptoms of AIP. In the case of acute abdominal pain with fever, the suspicion of appendicitis is obvious. An appendectomy scar is thus often found among patients diagnosed with porphyria.

Note: The cases of acute porphyria are often primarily treated surgically; thereby, anesthesia poses a great risk for the patients.

Neurologic-psychiatric symptoms of AIP are diverse and can occur in the form of peripheral nerve palsies, neuralgic pain, paresthesia, epilepsy, resentment, and psychos. A symptomatic triad is completed by the occurrence of **cardiovascular symptoms**, especially tachycardia and hypertension. AIP is **not associated with increased photosensitivity**.

Note: In cases of the triad of abdominal pain, neurologic-psychiatric symptoms, and tachycardia, a healthcare provider should always think about the differential diagnosis of porphyria.

Diagnosis and treatment of AIP

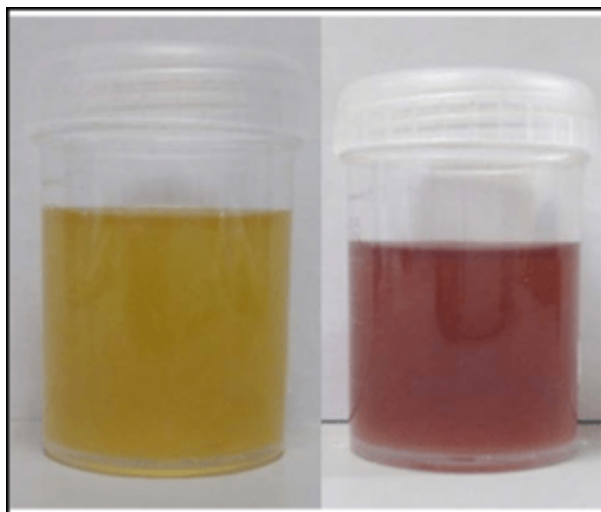


Image: Darkened urine after three days of light exposure. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/).

Even in this form, the anamnesis and symptoms are leading the way in the diagnosis, especially in the presence of the typical triad. In an acute episode, metabolites such as porphobilinogen and δ -aminolevulinic acid can be detected in blood and urine. Often, patients will produce discolored urine, which becomes discolored to dark red between acute attacks in 50% of cases when prolonged standing has occurred. Porphobilinogen can also be detected in stool.

Genetic tests are possible to confirm the diagnosis and determine the mutation. The

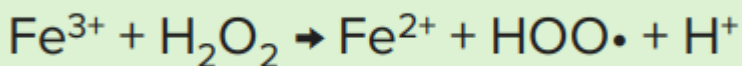
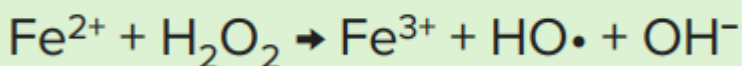
discontinuation of possible causative medication is therapeutically the top priority. In addition, the education of patients about possible triggers is very important. In order to treat the symptoms, healthcare providers often prescribe **harmless medications** such as beta blockers and paracetamol. A current list of medications classified as safe can be found on the Internet. Subsequently, the heme synthesis can be curbed with **glucose** and **heme arginate** instead of δ -aminolevulinic acid dehydratase. The use of heme arginate is also possible for relapse prevention. Treatment of the last choice is liver transplantation.

Secondary Porphyria

Secondary (i.e. acquired) porphyria can have various causes. Progressive **hepatocellular damage** can, for example, imitate the appearance of porphyria *cutanea tarda* through decreased enzyme activity. **Blood diseases, infections, and intoxications** continue to be probable causes. An important differential diagnosis of AIP is chronic lead poisoning. Lead inhibits δ -aminolevulinic acid dehydratase and ferrochelatase of heme synthesis and, in this way, leads to the accumulation of aminolevulinic acid and porphyrins, which can also be detected in urine. A test should be done for the diagnosis of **lead** in the blood.

Iron transport and storage

- Iron is a limiting micronutrient.
- Iron is needed for heme, enzymes, electron transport, and oxygen transport.
- Iron can gain or lose electrons, depending on the oxidative state.
- Iron is very reactive and toxic to cells.
- Iron can create radicals with the review of systems (ROS) in the cell via the Fenton reaction.



- Uptake into the body is tightly controlled, with no regulated means of excretion.
- Hemochromatosis occurs with an unregulated uptake of iron, with a genetic cause.
- It is most common among patients of Irish and Norwegian descent.
- Iron storage in cells is very carefully regulated.

Primary: genetic cause (0.6% of the population)	Secondary: acquired
	Cirrhosis of the liver
	Diabetes: deposition of iron in pancreas cells
	Cardiomyopathy
	Arthritis

Complications of porphyria

Long-term complications of porphyria include the following:

- Chronic hypertension
- Chronic kidney dysfunction
- Chronic pain syndrome
- Hepatocellular carcinoma

Prognosis of porphyria

- Repeated attacks of porphyria are associated with paresis.
- Erythropoietic porphyria is a severely crippling and painful disease that can affect the quality of life. It may lead to hepatocellular carcinoma.

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