

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; one clinically differentiates between acute and non-acute forms. In particular, a physician should also be aware of the two most common forms of overall rare diseases as an important differential diagnosis. Below is thus an overview of the clinical manifestations, diagnosis and treatment options of the porphyria.



Definition

Porphyria is a disease condition characterized by a defective heme synthesis pathway due to some enzyme defects, resulting in a clinical syndrome involving skin, nervous system, and liver at individual levels or cumulatively. It is considerable that heme production is a multi-level process controlled by various enzymes.

The Locations of the 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, the heme synthesis occurs

independently from each other, such that one speaks of heme pools here:

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

From the localization of the essential expression of the affected enzyme, it 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/)

The Pathogenesis of Porphyria

All porphyrias have the similarity in the pathogenesis, that an enzyme of the biosynthesis of the heme is impaired in its activity by a genetic defect. This results in an accumulation of the substrate of the affected enzyme. These intermediates can cause various organ damages and symptoms in increased concentrations. In addition, there is an increased excretion through the urine and stool. The allocation of the affected enzyme and type of porphyria following the steps of the heme synthesis is 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 III synthase	M Gunther
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; that is 5 cases/100,000 population. The incidence of symptoms of porphyria in Europe is 0.13 – 0.51 cases per million per year.
- The estimated risk of porphyria in Europe is 4%.

The Classification of Porphyrias

The 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 the porphyria cutanea tarda (PCT), the acute intermittent porphyria (AIP) and the erythropoietic protoporphyria (EPP). Other forms

such as the Doss-porphyrin for example, are extremely seldom.

1. Erythropoietic porphyria



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

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

2. Hepatic porphyria

3. Acute hepatic porphyria

- Acute intermittent porphyria (autosomal dominant).
- Hereditary coproporphyria (autosomal dominant).
- Porphyria variegata (autosomal dominant).
- Doss porphyria (autosomal recessive).

4. Chronic hepatic porphyria

Note: The Porphyria variegata is an acute, autosomal dominant inherited form of the 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 the metabolism, then the neurological region is mainly affected. If defects occur there at the final steps, then cutaneous involvement is there.

Clinical features

Some common signs and symptoms of porphyria are as follows:

- Acute colicky abdominal pain in the left lower abdomen which lasts for hours to days. Pain is rarely accompanied by fever, leukocytosis, or peritonitis. There is considerable discrepancy between a patient's clinical presentation of pain and objective findings.
- Nausea and vomiting.
- Muscular weakness.
- Limb pain.
- Quadriplegia.
- Pain in limbs.
- Psychiatric symptoms like 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 sign and symptoms in the absence of other obvious causes and urine examination. On urine examination, it is found that excretion of porphobilinogen (PBG) is increased 5-100 times.

The Porphyria Cutanea Tarda (PCT)

Aetiology and pathogenesis of the PCT

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

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

The symptoms of PCT

The most noticeable symptom of porphyria cutanea tarda is certainly the **photodermatosis**. The skin is extremely light sensitive and responds to exposure with blistering and delayed healing. Scars on the face and at the back of the hands can often be found. Similarly, patients show increased hair growth (**hypertrichosis**) and **hyperpigmentation**. The skin manifestation of the PCT can be presumed without prophylaxis disfiguring extent.



Image: "Erosions, crust, and blisters are evident on the hands of this patient with PCT" License: [CC BY 2.5](https://creativecommons.org/licenses/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 a dark-colored urine by porphyrins. This 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 the PCT

The diagnosis arises on the basis of anamnesis and symptoms, dark red or brownish discolored urine, a proven **porphyrinuria** and possibly a liver biopsy can be detected in the metabolites by fluorescence.

There is no causal treatment. The 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, medicamentous can be treated with **chloroquine**, which makes porphyrins complexed and renally excretable. In the case of 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 the liver damage.

The Acute Intermittent Porphyria (AIP)

Etiology and pathogenesis of AIP

The **second most common form** of porphyria is the acute intermittent porphyria (AIP). It is counted as the 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 a manifest porphyria. On the other hand, about a quarter of patients of non-family show de novo mutations. The affected enzyme is **porphobilinogen deaminase** with increase 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 include alcohol, metoclopramide, furosemide, diclofenac, ACE inhibitors, statins and many anesthetics such as barbiturates, among others.

The symptoms of the AIP

An acute porphyria syndrome is very diverse from the clinical presentation and often results in misdiagnoses. Leading the way are 3 main symptoms and the frequent association with intake of medication.

Abdominal discomfort with colicky pain and vomiting are a key symptom of the AIP. In the case of acute abdomen with fever, the suspicion of appendicitis is obvious. An appendectomy scar is thus often found amongst porphyria patients.

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

Neurological-psychiatric symptoms of an acute intermittent porphyria are diverse and can occur in the form of peripheral nerve palsies, neuralgic pains, paresthesias,

epilepsies, resentment and psychoses. The triad of **cardiovascular symptoms**, especially tachycardia and hypertension is completed. The acute intermittent porphyria is **not associated with increased photosensitivity**.

Note: In the case of the triad of abdominal pain, neurological-psychiatric symptoms and tachycardia, one should always think about the differential diagnosis of porphyria!

Diagnosis and treatment of the AIP

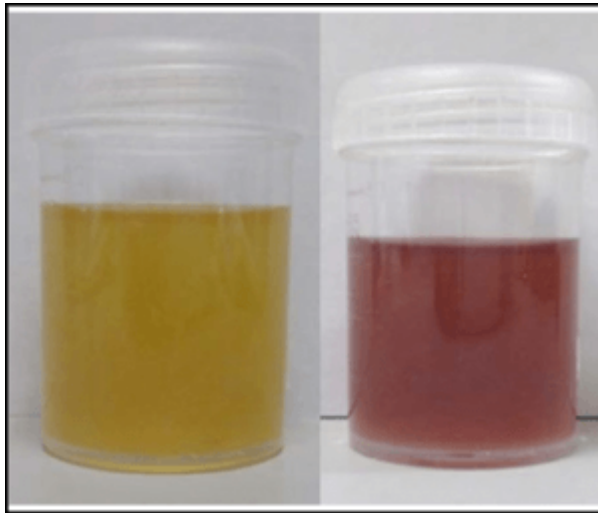


Image: "Darkend urine after 3 days of light exposure" License: [CC BY 3.0](#)

Even in this form, the anamnesis and symptoms are leading the way in the diagnostic, especially in the presence of the typical triad. In an acute episode, metabolites, such as porphobilinogen and δ -aminolevulinic acid, can be detected in the blood and urine. Often, one will also find discolored urine, which gets discolored into dark red between acute attacks in 50% of cases with prolonged standing. Porphobilinogen can also be detected in stool.

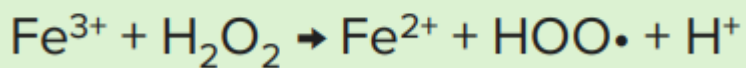
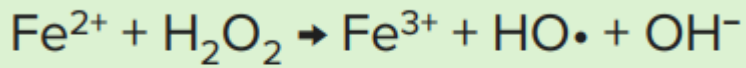
Genetic tests are possible to confirm the diagnosis and determine the mutation. The discontinuation of possible causative medication is therapeutically the top priority. Education of the patients about the possible triggers is very important here. In order to treat the symptoms, one resorts to **harmless medicines** 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** over the δ -aminolevulinic acid dehydratase. The use of heme arginate is also possible for relapse prevention. A measure of the last choice is a liver transplantation.

Secondary Porphyria

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

Iron Transport and Storage

- Iron is a limiting micro-nutrient.
- Needed for heme, enzymes, electron transport, and oxygen transport.
- Can gain or lose electrons, depending on the oxidative state.
- Very reactive and toxic to cells.
- Can create radicals with ROS in the cell via the Fenton reaction:



- Uptake into body tightly controlled — no regulated means of excretion.
- Hemochromatosis occurs with an unregulated uptake of iron — genetic cause.
- Most common among Irish and Norwegians.
- Iron storage in cells is very carefully regulated.

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

Complications of Porphyria

Long-term complications of porphyria include:

- 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, painful disease impacting the quality of life. It may lead to hepatocellular carcinoma.

Review Questions

The solutions can be found below the references.

1. Which medication is safe in the case of a patient with a suspected acute intermittent porphyria?

- A. Barbiturates for anesthesia of the patient.
- B. Metoclopramide for patients with vomiting.

- C. Furosemide.
- D. Beta-blockers for patients with tachycardia.
- E. Diclofenac for patients with pain.

2. Which of the porphyria has photosensitivity as the major symptom?

- A. The M. Gunther.
- B. The porphyria cutanea tarda.
- C. The acute intermittent porphyria.
- D. The Porphyria variegata.
- E. The Doss porphyria.

3. What is used for the treatment of an acute intermittent porphyria (AIP)?

- A. Protection from exposure to light.
- B. Heme arginate.
- C. Chloroquine.
- D. ACE inhibitor.
- E. Bloodletting therapy.

References

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Rassow et al: Duale Reihe Biochemie – Thieme Verlag, 2. Auflage

Deutsches Kompetenz-Zentrum für Porphyriadiagnostik und Konsultation
via www.porphyrie.com

The Drug Database for Acute Porphyria via drugs-porphyria.org

European Porphyria Network via porphyria-europe.com

Correct Answers: 1D, 2B, 3B

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Notes