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.

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.

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:

<table>
<thead>
<tr>
<th>Defective enzyme</th>
<th>Form of porphyria</th>
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<tbody>
<tr>
<td>δ-aminolevulinic acid synthase 2</td>
<td>X-chromosomal protoporphyria</td>
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<tr>
<td>δ-aminolevulinic acid dehydratase</td>
<td>Doss porphyria</td>
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<tr>
<td>Porphobilinogen deaminase</td>
<td><strong>Acute intermittent porphyria (AIP)</strong></td>
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<tr>
<td>Uroporphyrinogen III synthase</td>
<td>M Gunther</td>
</tr>
<tr>
<td>Uroporphyrinogen decarboxylase</td>
<td><strong>Porphyria cutanea tarda</strong></td>
</tr>
<tr>
<td>Coproporphyrinogen oxidase</td>
<td>Hereditary coproporphria</td>
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<tr>
<td>Protoporphyrinogen oxidase</td>
<td><strong>Porphyria variegata</strong></td>
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<tr>
<td>Ferrochelatase</td>
<td>Erythropoietic protoporphyria</td>
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The Classification of Porphyrias

The various types of porphyria are distinguished as followed. 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-porphyria for example, are extremely seldom.

1. **Erythropoietic porphyria**
- 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**
   - Porphyria cutanea tarda (autosomal dominant or acquired)

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

### 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.

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 the dark-colored urine by porphyrins. This is referred to as porphyrinuria.

Note: The most common localizations of skin damage caused by PCT are on 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 discoloured 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 avoidance of triggering noxae and consistent avoidance of light exposure. Repeated bloodletting can provide recovery through decreased erythrocyte count.

In addition medicamentous can be treated with chloroquine, which makes porphyrins complexed and renally excretable. In 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 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 hypoglycaemia, 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 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 porphyrina 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 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

Even in this form, the anamnesis and symptoms are leading the way in 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. 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 the 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, oxygen transport
- Can gain or lose electrons, depending on oxidative state
- Very reactive and toxic to cells
- Can create radicals with ROS in the cell via the Fenton reaction:

\[
Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\cdot + OH^- \\
Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO\cdot + H^+
\]

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

<table>
<thead>
<tr>
<th>Primary — genetic cause (0.6 % of population)</th>
<th>Secondary — acquired</th>
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<tbody>
<tr>
<td>Cirrhosis of liver</td>
<td></td>
</tr>
<tr>
<td>Diabetes — deposition of iron in pancreas cells</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
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</tbody>
</table>
Review Questions

The solutions can be found below the references.

1. Which medication is safe in 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 Porphyriediagnostik 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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