### 7.3 Porphyrias, Porphobilinogen, and δ-Aminolevulinic Acid

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#### 7.3.1 Introduction

Porphyrias are inborn errors of heme biosynthesis [1, 2]. There are seven steps in this metabolic pathway (Fig. 7.3.1), each of which may be affected, leading to a specific disease entity (Table 7.3.1). Heme is synthesized in each cell, as heme is the active group of several respiratory chain enzymes. The highest heme synthesis rate, however, is found in erythrocyte precursors in the bone marrow, and the second highest is found in the hepatocytes. Whereas the liver enzymes are the same housekeeping forms as those in other tissues, heme synthesis in erythrocyte precursor cells is differentially regulated. The initial enzyme erythrocytic δ-aminolevulinic acid (ALA) synthase (ALAS) is encoded by a gene different from the housekeeping one, and several other enzymes are regulated by alternate, erythrocyte-specific promoters [3–5]. The porphyrias are divided into two groups according to their clinical presentation: the acute porphyrias and the nonacute porphyrias [6]. Acute porphyrias are acute-intermittent porphyria (AIP), porphyria variegata (PV), hereditary coproporphyria (HC), and the rare ΑLΑ dehydratase (ALAD) deficiency. Acute porphyrias are characterized by episodes of severe abdominal pain, nausea, vomiting, constipation, psychic disturbances, tachycardia, hypertension, and hyponatremia, eventually progressing to muscular weakness, paresis (including respiratory muscles), epileptic seizures, coma, and death. These acute porphyrias are characterized by increases in urinary levels of ALA and porphobilinogen (PBG) of between 5- and 20-fold during the acute crises and for up to at least 7 days thereafter. Prepubertal children are rarely affected. Skin symptoms (blisters) may or may not be present. Nonacute porphyrias are characterized by skin symptoms that are limited to light-exposed areas. Two types of photodermatosis can be distinguished: (1) blisters of 1–2 cm in diameter, filled with clear liquid, fragility of skin and milia, or (2) acute, severely burning pain, in severe cases combined with pale swelling, fissures, and thickening of the dermis. The latter is observed mainly at the base knuckles of the hands. Discrete scars may be visible in the face. In all these forms, porphyrins are elevated in specific body fluids, but increases are eventually less dramatic than in acute porphyria episodes. The prevalent porphyrin pattern in conjunction with the clinical picture will enable diagnosis of a specific porphyria and to differentiate it from nonspecifically elevated porphyrins induced by a variety of factors such as alcohol intake and stress (see Table 7.3.1) [2].
### Table 7.3.1 Synopsis of the relatively frequent porphyrias. The diagnostic tests most significant for each porphyria have a gray background. The order of test to be applied depends on the clinical situation and has been outlined in the Introduction under the subheading diagnostic strategies (section 7.3.1.1).

<table>
<thead>
<tr>
<th>MIM Nr</th>
<th>ALAD deficiency</th>
<th>AIP</th>
<th>CEP</th>
<th>PCT</th>
<th>HC</th>
<th>PV</th>
<th>EPP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125 270</td>
<td>176 000</td>
<td>263 700</td>
<td>176 090/176 100</td>
<td>121 300</td>
<td>176 200</td>
<td>177 000</td>
</tr>
</tbody>
</table>

**Affected enzyme**

- ALA-dehydratase
- Hydroxymethylbilane synthase
- Uroporphyrinogen III synthase
- Uroporphyrinogen decarboxylase
- Coproporphyrinogen oxidase
- Protoporphyrinogen oxidase
- Ferrochelatase

**Clinical symptoms**

- Photosensitivity
- Abdominal pain

**Urine**

- ALA: ↑↑, ↑, None
- PBG: Normal, ↑↑, ↑, ↑, ↑↑, ↑↑, ↑↑, Normal
- Uro: Normal, ↑↑, ↑↑, ↑, ↑, ↑↑, Normal
- Intermediaries: Normal, ↑↑, ↑↑, Normal

**Feces**

- Copro I: Normal–(↑), Normal–, Normal
- Copro III: Normal–(↑), Normal–, Normal
- Ratio: <2, <2, >2, >2
- Proto: Normal–(↑), Normal

**Erythrocytes**

- Uro, Copro: ↑↑, ↑, Normal

**Additional tests**

- ALAD activity ↓
- HMBS activity ↓
- Isomer separation
- Isocoproporphyrin
- Plasma scan