Module 01

Classification of Porphyria
Porphyria—A Rare Disease of Clinical Consequence

• Porphyria is a group of at least 8 metabolic disorders\(^1,2\)
  – Each subtype of porphyria involves a genetic defect in a heme biosynthesis pathway enzyme\(^1,2\)
  – The subtypes of porphyria are associated with distinct signs and symptoms in patient populations that can differ by gender and age\(^1,3\)

• Prevalence of some subtypes of porphyria may be higher than generally assumed\(^3\)

### Estimated Prevalence of Most Common Subtypes of Porphyria\(^1,4\)

<table>
<thead>
<tr>
<th>Subtype of Porphyria</th>
<th>Estimated Prevalence Based on European and US Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyria cutanea tarda (PCT)</td>
<td>1/10,000 (EU)(^1)</td>
</tr>
<tr>
<td>Acute intermittent porphyria (AIP)</td>
<td>0.118-1/20,000 (EU)(^1,4) 5/100,000 (US)(^1)</td>
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<tr>
<td>Erythropoietic protoporphyria (EPP)</td>
<td>1/50,000-75,000 (EU)(^1)</td>
</tr>
</tbody>
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Classification of Porphyria

Porphyria can be classified in 2 major ways\(^1,2\):

1. According to major physiological sites: liver or bone marrow\(^1,2\)
   - Heme precursors originate in either the liver or bone marrow, which are the tissues most active in heme biosynthesis\(^1,2\)

2. According to major clinical manifestations\(^1,2\)
   - Acute Versus Photocutaneous Porphyria
     - Major clinical manifestations are either neurovisceral symptoms (eg, severe, diffuse abdominal pain) associated with acute exacerbations or cutaneous lesions resulting from phototoxicity\(^1,2\)
     - *Acute* hepatic porphyria may be somewhat of a misnomer since the clinical features may be prolonged and chronic\(^3\)

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Using Major Clinical Manifestations for Classification of 8 Porphyria Subtypes


**Acute Hepatic Porphyria:**

Cardinal Manifestation of Acute Neurovisceral Symptoms

The symptoms of AHP are caused by increased concentrations of the neurotoxic intermediates ALA and PBG that accumulate due to enzyme deficiencies in the heme biosynthesis pathway, leading to nervous system injury.

**Photocutaneous Porphyria:**

Cardinal Manifestation of Skin Lesions

The symptoms of photocutaneous porphyria are caused by increased concentrations of the photosensitizing porphyrins.

HCP and VP are associated with both acute neurovisceral symptoms and skin lesions.

ADP=aminolevulinic acid dehydratase-deficiency porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; CEP=congenital erythropoietic porphyria; EPP=erythropoietic protoporphyria; HCP=hereditary coproporphyria; PBG=porphobilinogen; PCT=porphyria cutanea tarda; VP=variegate porphyria; XLDP=X-linked dominant protoporphyria.
Heme Biosynthesis Pathway, Defective Enzymes, and Related Porphyria

The Rate-Limiting Step for the Pathway is the Formation of ALA, Catalyzed by ALAS1

Enzymes: ALAS1, ALAD, PBGD/HMBS, UROS, UROD, CPOX, PPOX, FECH

Heme Synthesis Pathway with Intermediaries:
- Glycine
- Succinyl CoA
- Aminolevulinic acid (ALA)
- Porphobilinogen (PBG)
- Hydroxymethylbilane (HMB)
- Uroporphyrinogen (URO III)
- Coproporphyrinogen (COPRO III)
- Protoporphyrinogen (PROTO'gen IX)
- Protoporphyrin (PPIX)
- Heme

Acute Hepatic Porphyria:
- ADP (ALAD-deficiency porphyria)
- AIP (acute intermittent porphyria)
- CEP (congenital erythropoietic porphyria)
- PCT (porphyria cutanea tarda)
- HCP (hereditary coproporphyria)
- VP (variegate porphyria)

Photocutaneous Porphyria:
- XLDPP (X-linked dominant protoporphyria)
- EPP (erythropoietic protoporphyria)

The Prevalence of the Four Different Subtypes of AHP

<table>
<thead>
<tr>
<th>Subtype of AHP</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP (Acute Intermittent Porphyria)</td>
<td>0.118-1/20,000 (EU*)²,³ - 5/100,000 (US*)³</td>
</tr>
<tr>
<td>HCP (Hereditary Coproporphyria)</td>
<td>2/1,000,000 (Denmark*)³</td>
</tr>
<tr>
<td>VP (Variegate Porphyria)</td>
<td>3.2/1,000,000 (EU*)²</td>
</tr>
<tr>
<td>ADP (Aminolevulinic Acid Dehydratase-Deficiency Porphyria)</td>
<td>6 cases of ADP reported worldwide at time of publication³</td>
</tr>
</tbody>
</table>

- AIP accounts for about 80% of AHP cases⁴
- The prevalence of AIP may be underreported due to estimates based on patients with symptomatic disease only rather than an enzyme mutation⁵
  - There is even less information about the other subtypes of AHP

*Prevalence data from these particular countries were cited due to ongoing research and relatively high prevalence.

AHP is a Genetic Disease with a Combination of Hormonal and Environmental Precipitating Factors

- Acute exacerbations in genetically predisposed patients are frequently preceded by environmental or hormonal precipitating factors\(^1\)\(^2\)\(^4\):
  - When manifested, the disease can be debilitating and even life threatening\(^5\)
- Signs and symptoms are predominant in women of reproductive age but can occur in men as well\(^3\):
  - It is rare to experience AHP symptoms before puberty\(^6\)
  - Exacerbations are less likely after menopause\(^2\)
- There is higher prevalence in Caucasians, especially northern Europeans, but AHP can occur in all races and ethnic groups\(^4\)\(^7\)

- Hormonal and environmental precipitating factors of AHP exacerbations\(^1\)\(^2\)\(^4\):
  - Woman’s menstrual cycle
  - Many drugs metabolized by CYP450 enzymes (eg, barbiturates, synthetic progestins, sulfonamide antibiotics)
  - Crash dieting
  - Cigarette smoking
  - Excessive alcohol use
  - Infections and surgery
  - Psychological stress

Definition and classification of porphyria

- Porphyria is a group of at least 8 metabolic disorders caused by alterations in enzymes involved in the heme biosynthesis pathway\(^1\)

- Categorized as AHP or photocutaneous porphyria based on clinical manifestations\(^2\)
  - The signs and symptoms of AHP are due to increased levels of the neurotoxic intermediates ALA and PBG, leading to nervous system injury\(^2\)
  - The signs and symptoms of photocutaneous porphyria are caused by increased levels of photosensitizing porphyrins\(^2\)

Is the prevalence of AHP higher than thought?

- The combined prevalence of AHP subtypes has been estimated to be approximately 5 cases/100,000\(^3\)
- However, the prevalence of AHP may be higher than current estimates because these estimates are usually limited to those with symptomatic disease\(^4\)
- AHP is also associated with delayed diagnosis and misdiagnosis\(^3\)

AHP associated with debilitating and life-threatening signs and symptoms

- The cardinal presentation of AHP is severe, diffuse abdominal pain and other signs and symptoms (eg, nausea/vomiting, limb pain/weakness) that can progress to neurologic damage and even death\(^3\)
- The term acute hepatic porphyria does not capture the frequent prolonged and chronic clinical features of this disease\(^3\)

Summary