Acute Hepatic Porphyria (AHP): Simplifying the Diagnostic Path
“Zebra” is a medical school colloquialism that is used to describe a relatively rare diagnosis. It originates from the saying “When you hear hoofbeats behind you, don’t expect to see a zebra” attributed to Theodore Woodward, MD, a former professor at the University of Maryland School of Medicine in Baltimore in the late 1940s. He explained that since horses are more common hoofed animals, one would naturally assume that the hoofbeats belong to a horse and not a zebra.

Overview of the Diagnostic Challenges of AHP

The Challenge of Diagnosing AHP

- Multisystem signs and symptoms of AHP can resemble those of other diseases, complicating diagnosis\(^1,2\)
- Acute exacerbations of severe, diffuse abdominal pain often lead patients to first present to the emergency department (ED), where AHP is often overlooked in differential diagnosis\(^1,3\)
- Diagnosis of AHP can be delayed for up to 15 years and can involve multiple hospitalizations and even unnecessary surgeries\(^1,4\)

Factors That Can Facilitate a Diagnosis of AHP

- Recognizing a cluster of signs and symptoms can facilitate diagnosis\(^5\)
- Earlier recognition of AHP can occur if healthcare providers examine the patient history of neurovisceral/GI symptoms along with the following\(^6\):
  - Hospitalizations and repeated ED visits without definitive diagnosis
  - Necessity for repeated opioid analgesic prescriptions to relieve pain

Most Common Signs and Symptoms of an Acute Exacerbation

• Signs and symptoms of AHP* include\(^1\-3\):

Over 90% of patients with AHP report abdominal pain (mimics an acute abdomen but without specific localization)\(^1\,2\)

*There are 4 AHP subtypes. About 80% of cases are acute intermittent porphyria (AIP), followed by hereditary coproporphyria (HCP), variegate porphyria (VP), and the extremely rare ALA dehydratase-deficiency porphyria (ADP)\(^1\,2\,4\)

\(^{1}\)Cutaneous symptoms occur only in HCP and VP\(^1\,3\)

Chronic Symptoms Can Occur in Some Patients with AHP

Methods
- EXPLORE study—an observational, multinational, prospective, natural history study of 112 people living with recurrent exacerbations of AHP
- Key eligibility criteria
  - ≥3 exacerbations per year or use of prophylactic treatment

Results
- 46% of patients reported daily symptoms
- 65% of patients reported chronic symptoms in between frequent attacks
  - Some of these patients were treated with hemin or opioid prophylaxis

<table>
<thead>
<tr>
<th>Pain</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>0</td>
</tr>
<tr>
<td>Other pain</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
</tr>
<tr>
<td>Back pain</td>
<td>20</td>
</tr>
<tr>
<td>Arm/leg pain</td>
<td>25</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>25</td>
</tr>
<tr>
<td>Skin pain</td>
<td>30</td>
</tr>
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<table>
<thead>
<tr>
<th>Mood/Sleep</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>5</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>10</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>15</td>
</tr>
<tr>
<td>Feeling sad</td>
<td>20</td>
</tr>
<tr>
<td>Feeling unmotivated</td>
<td>25</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>30</td>
</tr>
<tr>
<td>Other mood/sleep</td>
<td>30</td>
</tr>
<tr>
<td>Feeling disoriented</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Feeling thirsty</td>
<td>20</td>
</tr>
<tr>
<td>Heartburn</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
</tr>
<tr>
<td>Other digestive</td>
<td>35</td>
</tr>
<tr>
<td>Weakness</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in urine color</td>
<td>0</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Fast heart beat</td>
<td>10</td>
</tr>
<tr>
<td>Shakiness</td>
<td>15</td>
</tr>
<tr>
<td>Blisters/rashes</td>
<td>20</td>
</tr>
<tr>
<td>Chills/fever</td>
<td>25</td>
</tr>
<tr>
<td>Sweating</td>
<td>30</td>
</tr>
</tbody>
</table>

Bonkovsky HL et al. AASLD 2018. Poster.
AHP Can Be Misdiagnosed as More Commonly Encountered Conditions

Other gastrointestinal disorders
- Crohn’s disease
- Irritable bowel syndrome (IBS)
- Acute gastroenteritis with vomiting
- Hepatitis

Neurological/neuropsychiatric disorders
- Fibromyalgia
- Guillain-Barré syndrome
- Psychosis

Gynecological disorders
- Endometriosis

Acute abdomen conditions
- Appendicitis
- Cholecystitis
- Peritonitis
- Pancreatitis
- Intestinal occlusion

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## Differentiating Abdominal Pain Associated with AHP from Other More Common GI Conditions

<table>
<thead>
<tr>
<th>Location</th>
<th>CONDITIONS</th>
</tr>
</thead>
</table>
| **Right Upper Quadrant Pain** | • Pancreatitis  
• Cholecystitis  
• Hepatitis |
| **Left Upper Quadrant Pain** | • Pancreatitis  |
| **Right Lower Quadrant Pain** | • Inflammatory bowel disease (IBD)  
• IBS  
• Appendicitis |
| **Left Lower Quadrant Pain** | • IBD  
• IBS |
| **Any location** | • Intestinal obstruction  
• Peritonitis |

**AHP Acute Abdominal Pain**
- Severe, diffuse, unremitting abdominal pain without fever or leukocytosis

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Mistaking AHP for More Common Neurologic Conditions

AHP Cases Misdiagnosed as Polyneuropathy or Encephalopathy

108 neurological patients with symptoms suggestive of AHP, but not previously diagnosed with AHP, were prospectively evaluated for urinary porphyrins and their precursors

- Symptoms included abdominal pain, dysautonomia, polyneuropathy, mental symptoms, and seizures

11% of patients were found to have previously undiagnosed AHP, based on urinary PBG levels

PBG=porphobilinogen.
Common Features of AHP Patients

Demographics

- AHP occurs most frequently in women of reproductive age\(^1\)
  - Rare for signs and symptoms to occur before puberty\(^1\), although diagnosis can be delayed until after reproductive age

- AHP can occur in men as well as women\(^2,3\)
  - In one study, 17% of men and 83% of women had AIP\(^2\)

- AHP can occur across all ethnic and racial groups\(^3\)
  - AHP most common in Caucasians\(^2,4\)
  - AHP can be found with greater prevalence in certain geographic areas, such as Sweden, Nova Scotia, and South Africa, due to a founder effect where the genetic mutation(s) of a common ancestor gets amplified due to isolation\(^5-8\)

Initial clinical features of exacerbations

- Several days of severe fatigue and inability to concentrate\(^1\)
  - Followed by progressively worsening abdominal pain, nausea and vomiting, and subtle neurologic signs
  - Weakness, unpleasant sensations, and altered affect

Previous history

- Past visits to ED with similar symptoms and nondiagnostic evaluation\(^1\)

Signs and Symptoms of AHP Usually Occur in Genetically Predisposed Patients Exposed to Precipitating Factors

Online resource for clinicians


Description

- A website that allows clinicians to fill in a generic or brand drug name to determine if the drug is safe to use in patients with porphyria

Note: This database provides information on drugs that may be unsafe in patients with AHP. This website is not owned or controlled by Alnylam Pharmaceuticals, Inc.

<table>
<thead>
<tr>
<th>Precipitating Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women’s Natural Hormonal Cycle</strong>&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>• Symptoms can be precipitated by the luteal phase of the menstrual cycle where increased levels of progestins are seen</td>
</tr>
</tbody>
</table>
| **Prescription Drugs Shown to Induce Aminolevulinic Acid Synthase 1 (ALAS1)**<sup>1,2</sup> | • Oral contraceptives  
• Progestins  
• Various anticonvulsant agents  
• Sulfonamides |
| **Diet**<sup>1-4</sup>                                   | • Crash dieting  
• Severe restriction of calories or carbohydrates |
| **Lifestyle Factors**<sup>4,5</sup>                      | • Smoking  
• Excessive alcohol consumption |
| **Infections and Surgery**<sup>1,2,4,5</sup>              | • Due to increase in metabolic stress |
| **Psychological Stress**<sup>4,5</sup>                   | • Both men and women noted psychological stress as a triggering factor in a population-based study in Sweden<sup>4</sup> |

The Biochemical Diagnosis of AHP

- Spot urine test for porphobilinogen (PBG), delta-aminolevulinic acid (delta-ALA), and porphyrins is used for diagnosis of AHP\(^1\)-\(^3\)
  - In the 3 most common subtypes of AHP (AIP, HCP, VP), exacerbations are accompanied by a clear increase in PBG\(^3\)
- Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP\(^3\)
  - Urine porphyrins can help differentiate between AHP subtypes\(^2\)
  - Ordering lab tests for urine porphyrins does not include assessment of PBG/delta-ALA or their corresponding levels\(^3\)
- PBG and ALA may remain elevated during recovery from an AIP or other type of AHP exacerbation\(^3\)-\(^5\)

<table>
<thead>
<tr>
<th>Spot Urine Test</th>
<th>CPT Code</th>
<th>Laboratory Values by AHP Subtypes During Exacerbation(^1,6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBG</td>
<td>84110</td>
<td>Increased</td>
</tr>
<tr>
<td>Delta-ALA</td>
<td>82135</td>
<td>Increased</td>
</tr>
<tr>
<td>Porphyrins</td>
<td>84120</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Genetic Testing for AHP

- Once a diagnosis of AHP is biochemically confirmed, gene sequencing can be used to identify the mutation and AHP subtype\(^1\)
- Alnylam Pharmaceuticals sponsors no-charge, third-party genetic testing and counseling* for individuals who may carry gene mutations known to be associated with AHP
  - Healthcare professionals must confirm that patients meet certain criteria to use the program
  - To find out more information about Alnylam Act®, visit: https://www.alnylam.com/medical-professional-resources/genetic-testing-counseling/porphyrin-testing-counseling/

*Genetic testing is available in the US and Canada. Genetic counseling is only available in the US.


<table>
<thead>
<tr>
<th>AHP Subtype(^1,^2)</th>
<th>Mutations in Genes Encoding Deficient Enzymes(^1,^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>Hydroxymethylbilane synthase (HMBS)</td>
</tr>
<tr>
<td>HCP</td>
<td>COPROgen oxidase (CPOX)</td>
</tr>
<tr>
<td>VP</td>
<td>PROTOgen oxidase (PPOX)</td>
</tr>
<tr>
<td>ADP</td>
<td>ALA dehydratase (ALAD)</td>
</tr>
</tbody>
</table>

\(^1\) Mutations in Genes Encoding Deficient Enzymes

\(^2\) AHP Subtype
A Summary of the Diagnostic Journey

**Family history of AHP (often unknown)/patient presentation**

Hallmark symptom: severe, diffuse abdominal pain (neurovisceral pain) with no fever or leukocytosis¹⁻³
- Nausea/vomiting, limb weakness or pain, anxiety, confusion, or skin lesions on sun-exposed areas (HCP and VP only) can also occur³

**Patient history**

Patient characteristics
- Gender: AHP more common in females of reproductive age but can also occur in males³,⁴
  - In one study, 17% of men and 83% of women had AIP⁴
- Race: AHP most common in Caucasians, especially northern Europeans, but can occur in all races²,⁴,⁵

Possible precipitating factors¹⁻³
- Women's natural hormonal cycle
- Prescription drugs that induce ALAS1
- Crash dieting/severe restriction of calories or carbohydrates
- Other factors

**Diagnostic tests**

- PBG/delta-ALA/porphyrins spot urine test¹,²
  - Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP²
- DNA testing for diagnostic confirmation and identification of AHP subtype¹

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Summary—the Benefits of Prompt Diagnosis

AHP can be misdiagnosed as more commonly evaluated conditions

- AHP: a group of rare genetic diseases whose cardinal signs and symptoms—such as severe, diffuse abdominal pain—can resemble those of other more common conditions.

- Recognizing a cluster of signs and symptoms as well as healthcare utilization patterns should raise suspicion of AHP.

The importance of prompt diagnosis

- Prompt diagnosis during acute exacerbations of AHP may spare patients multiple hospitalizations and unnecessary surgeries.

Simple biochemical diagnostic test

- The prompt use of a simple spot urine test for delta-ALA/PBG/porphyrins facilitates the differential diagnosis of AHP.

- Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP.

- In the 3 most common subtypes of AHP, exacerbations are accompanied by a clear increase in PBG, which can conveniently be measured in urine.