



MODULE  
**03**

# Acute Hepatic Porphyria (AHP): Simplifying the Diagnostic Path



## AHP: Rare Disease With Clinical Clues That Can Help With Diagnosis

“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 because horses are more common hooved animals, one would naturally assume that the hoofbeats belong to a horse and not a zebra.



**Reference: 1.** Medical zebra. The EPIC (Empowering People With Invisible Chronic Illness) Foundation website. Accessed June 7, 2021. <http://www.epictogether.org/medical-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<sup>1,2</sup>
- Acute attacks of severe, diffuse abdominal pain often lead patients to first present to the emergency department (ED), where AHP is often overlooked in differential diagnosis<sup>1,3</sup>
- Diagnosis of AHP can be delayed for up to 15 years and can involve multiple hospitalizations and even unnecessary surgeries<sup>1,4</sup>

## Factors That Can Facilitate a Diagnosis of AHP

- Frequent doctor visits, including primary care physicians and specialists<sup>5</sup>
  - 89% of patients with AHP have seen a specialist at least every 12 months, with 36% of them seeing one at least monthly<sup>5\*</sup>
- Continued symptomatology after treatment and/or surgical intervention (eg, cholecystectomy or appendectomy)<sup>4,6</sup>
- An impression of psychosomatic pain or drug addiction due to lack of objective findings or poor response to analgesics<sup>3</sup>
- Recurrent pain during the luteal phase of the menstrual cycle<sup>6</sup>

\*12-month results from EXPLORE, a prospective natural history study of patients (N=112) who experienced recurrent AHP attacks ( $\geq 3$ /year) or received prophylactic treatment.<sup>5</sup>

**References:** 1. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3(1):17-26. 2. Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368. 3. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 4. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 5. Gouya L et al. ICPP 2017. Presentation OC13. 6. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450.

# AHP\* Features a Broad Range of Symptoms

## SEVERE, DIFFUSE ABDOMINAL PAIN<sup>1,2</sup>



### 1 OR MORE OF THE FOLLOWING<sup>1-5</sup>

AUTONOMIC Nervous System <sup>1,2</sup>	CENTRAL Nervous System <sup>1,3</sup>	PERIPHERAL Nervous System <sup>1,2</sup>	CUTANEOUS <sup>2</sup>	OTHER Common AHP Symptoms <sup>2,5</sup>
<ul style="list-style-type: none"><li>• Nausea/vomiting</li><li>• Constipation</li><li>• Tachycardia</li><li>• Systemic arterial hypertension</li></ul>	<ul style="list-style-type: none"><li>• Seizures</li><li>• Anxiety</li><li>• Mental status changes</li></ul>	<ul style="list-style-type: none"><li>• Limb weakness or pain</li><li>• Peripheral neuropathy</li></ul>	<ul style="list-style-type: none"><li>• Skin lesions on sun-exposed areas (Cutaneous symptoms primarily occur in HCP and VP.)</li></ul>	<ul style="list-style-type: none"><li>• Hyponatremia</li><li>• Dark, reddish urine</li></ul>



# >90%

of patients with AHP who experience recurrent attacks report abdominal pain (mimics an acute abdomen but without specific localization)<sup>1,2,6</sup>

AHP=acute hepatic porphyria.

\*There are 4 types of AHP. Over 80% of cases are acute intermittent porphyria (AIP), followed by variegate porphyria (VP), hereditary coproporphyria (HCP), and the extremely rare ALAD-deficiency porphyria (ADP).<sup>4,7</sup>

**References:** 1. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. 2. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 3. Puy et al. *Lancet.* 2010;375(9718):924-937. 4. Simon A et al. *Patient.* 2018;11:527-537. 5. Balwani M et al. *Hepatology.* 2017;66:1314-1322. 6. Gouya et al. *Hepatology.* 2020;71(5):1546-1558. 7. Bissell DM et al. *N Engl J Med.* 2017;377(9):862-872.

# Symptoms of AHP Can Occur Chronically, Between Attacks

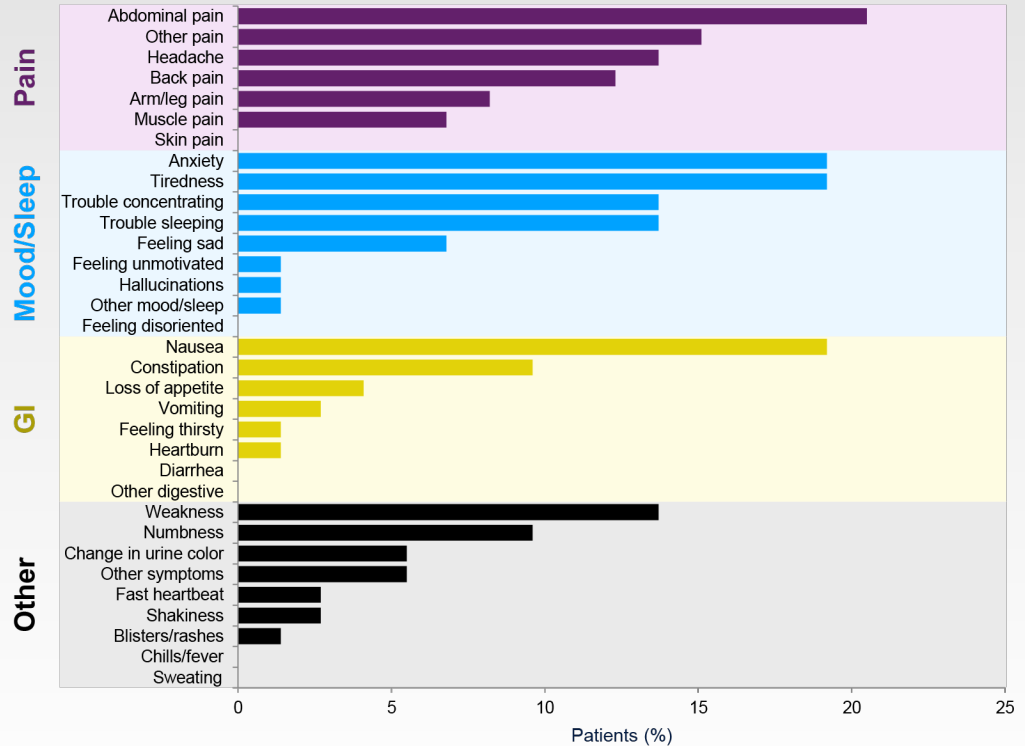
## Methods

- EXPLORE study—an observational, multinational, prospective, natural history study of 112 people living with recurrent attacks of AHP<sup>1</sup>
- Key eligibility criteria
  - ≥3 attacks per year or use of prophylactic treatment<sup>1</sup>

## Results

- 65% of patients reported chronic symptoms in between attacks (including pain)<sup>1</sup>
  - Some of these patients were treated with hemin or opioid prophylaxis<sup>1</sup>
- 46% of patients reported experiencing chronic symptoms every day<sup>1</sup>

Chronic Symptoms Experienced Between AHP Attacks (n=73)<sup>1</sup>



Reference: 1. Gouya L et al. *Hepatology*. 2020;71:1546-1558.

# AHP Is Often Misdiagnosed Due to Nonspecific Symptoms

Some potential misdiagnoses include:



## Gastrointestinal disorders<sup>1-3</sup>

Irritable bowel syndrome (IBS)  
Acute gastroenteritis with vomiting  
Hepatitis



## Neurological/neuropsychiatric disorders<sup>1,3,4</sup>

Fibromyalgia  
Guillain-Barré syndrome  
Psychosis



## Gynecological disorder<sup>3</sup>

Endometriosis



## Acute abdomen conditions<sup>1,5,6</sup>

Appendicitis  
Cholecystitis  
Peritonitis  
Pancreatitis  
Intestinal occlusion

**References:** 1. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. 2. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. 3. Ko JJ et al. ACG 2018. Poster. 4. Meyer UA et al. *Semin Liver Dis.* 1998;18:43-52. 5. Alfadhel M et al. *Neuropsychiatr Dis Treat.* 2014;10:2135-2137. 6. Kondo M et al. *Int J Hematol.* 2004;79:448-456.

# Differentiating Abdominal Pain Associated With AHP From Other More Common GI Conditions

## Right Upper Quadrant Pain<sup>1</sup>

- Cholecystitis
- Hepatitis

## Left Upper Quadrant Pain<sup>1</sup>

- Pancreatitis

## Right Lower Quadrant Pain<sup>1</sup>

- Inflammatory bowel disease (IBD)
- Irritable bowel syndrome (IBS)
- Appendicitis

## Left Lower Quadrant Pain<sup>1</sup>

- IBD
- IBS

## Any location<sup>1</sup>

- Intestinal obstruction
- Peritonitis

## ***AHP Acute Abdominal Pain***

- Severe, diffuse, unremitting abdominal pain without fever or leukocytosis<sup>2</sup>

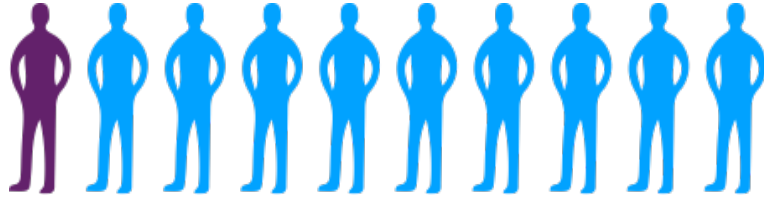
**References:** 1. Cartwright SL, Knudson MP. *Am Fam Physician*. 2008;77:971-978. 2. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

# Mistaking AHP for More Common Neurologic Conditions

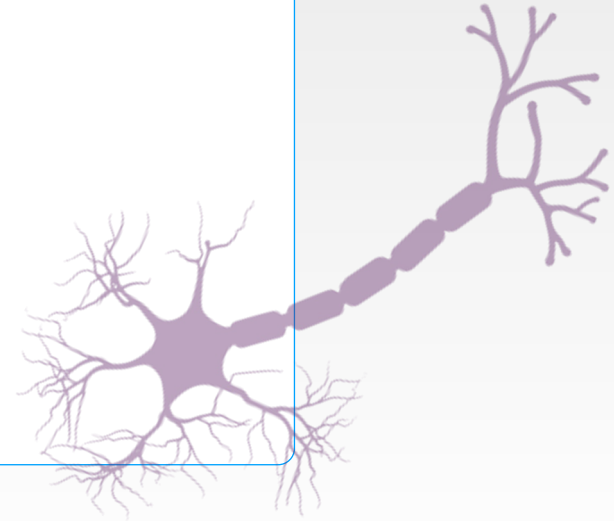
## AHP Cases Misdiagnosed as Polyneuropathy or Encephalopathy

108 neurological patients with symptoms suggestive of AHP, but not previously diagnosed with AHP, were prospectively evaluated for urinary PBG (porphobilinogen), ALA (aminolevulinic acid), and porphyrins

- Symptoms included abdominal pain, dysautonomia, polyneuropathy, mental symptoms, and seizures<sup>1</sup>



**11%** of patients were found to have previously undiagnosed AHP, based on urinary PBG levels<sup>1</sup>



PBG=porphobilinogen.

Reference: 1. Pischik E et al. *J Neurol.* 2008;255:974-979.



# Some Common Features of Patients With AHP

## Demographics

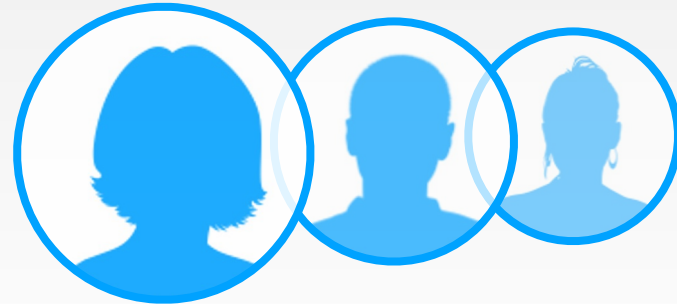
- AHP occurs most frequently in women of reproductive age<sup>1</sup>
  - Rare for signs and symptoms to occur before puberty,<sup>1</sup> although diagnosis can be delayed until after reproductive age
- AHP can occur in men as well as women<sup>2,3</sup>
  - In one study, 17% of men and 83% of women had AHP<sup>2</sup>
- AHP can occur across all ethnic and racial groups<sup>3</sup>
  - 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<sup>5-8</sup>

## Initial clinical features of attacks

- Several days of severe fatigue and inability to concentrate<sup>1</sup>
  - 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<sup>1</sup>



**References:** 1. Bissell DM et al. *N Engl J Med.* 2017;377:862-872. 2. Bonkovsky HL et al. *Am J Med.* 2014;127:1233-1241. 3. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. 4. Bonkovsky HL AASLD 2018. Poster. 5. Elder G et al. *J Inherit Metab Dis.* 2013;36:849-857. 6. Lee J-S, Anvret M. *Proc Natl Acad Sci USA.* 1991;88:10912-10915. 7. Greene-Davis ST et al. *Clin Biochem.* 1997;30:607-612. 8. Warnich L et al. *Hum Mol Genet.* 1996;5:981-984.

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

Precipitating Factor	Women's Natural Hormonal Cycle <sup>1-4</sup>	Prescription Drugs Shown to Induce Aminolevulinic Acid Synthase 1 (ALAS1) <sup>1,2*</sup>	Diet <sup>1-4</sup>	Lifestyle Factors <sup>4,5</sup>	Infections and Surgery <sup>1,2,4,5</sup>	Psychological Stress <sup>4,5</sup>
Comment	Symptoms can be precipitated by the luteal phase of the menstrual cycle where increased levels of progestins are seen	<ul style="list-style-type: none"> <li>Anesthetics</li> <li>Antimicrobials</li> <li>Oral contraceptives</li> <li>Hormones</li> <li>Anticonvulsants</li> <li>Migraine drugs</li> <li>Antihistamines</li> <li>Sedatives</li> <li>Antihyperglycemics</li> </ul>	<ul style="list-style-type: none"> <li>Extreme dieting</li> <li>Severe restriction of calories or carbohydrates</li> </ul>	<ul style="list-style-type: none"> <li>Smoking</li> <li>Excessive alcohol consumption</li> </ul>	Due to increase in metabolic stress	Both men and women noted psychological stress as a triggering factor in a population-based study in Sweden <sup>4</sup>

\*The American Porphyria Foundation Drug Database (<http://www.porphyrifoundation.com/drug-database>) and United Porphyrias Association Drug Safety Database information (<https://www.porphyrria.org/patient-resources/drug-safety-database-for-ahp/>) allows clinicians to gather information to help determine if the drug is safe to use in patients with porphyria. This database is developed and maintained by the American Porphyria Foundation. Alnylam Pharmaceuticals does not endorse and is not responsible for the content on the sites that are not owned and operated by Alnylam.

**References:** 1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 2. Bissell DM et al. *N Engl J Med.* 2017;377:862-872. 3. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. 4. Bylesjö I et al. *Scand J Clin Lab Invest.* 2009;69:612-618. 5. Pischik E, Kauppinen R. *Appl Clin Genet.* 2015;8:201-214.

# Biochemical Testing for AHP

- Random (spot) urine tests are the primary method to diagnosis AHP<sup>1</sup>
- A PBG random (spot) urine test can detect elevated levels of PBG when a patient is symptomatic<sup>2</sup>
- Substantial elevation of urinary PBG is a hallmark indicator of 3 types of AHP: acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP)<sup>1,2</sup>
- An ALA random (spot) urine test can help diagnose ALAD-deficiency porphyria—an extremely rare type of AHP<sup>2</sup>
- The optimal time to test is during or shortly after an attack when ALA and PBG levels have spiked, because levels may fall when symptoms resolve<sup>2-4</sup>

Random (Spot) Urine Test	CPT Code	Laboratory Results by AHP Types During an Attack <sup>1,4</sup>			
		Acute Intermittent Porphyria (AIP)	Hereditary Coproporphyria (HCP)	Variegate Porphyria (VP)	ALAD-Deficiency porphyria
PBG	84110	Increased	Increased	Increased	No increase
Delta-ALA	82135	Increased	Increased	Increased	Increased
Porphyrins	84120	Increased uroporphyrin	Increased coproporphyrin (COPRO)	Increased COPRO	Increased COPRO

Tests are more accurate when sample is collected during acute episodes; ALA and PBG should be normalized to creatinine in order to adjust for differences in the degree of urinary concentration; 24-hour urine collection is generally not required; samples typically should be light-protected and frozen/refrigerated based on lab specifications. Contact your local lab for their specific requirements. Additional testing (genetic or biochemical) is typically required to differentiate AHP type (AIP, HCP, VP, or ADP).

**References:** 1. Wang B, et al. *Gastroenterology*. 2023;164(3):484-491. 2. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. 3. Balwani M et al. *Hepatology*. 2017;66:1314-1322. 4. Ventura P et al. *Eur J Intern Med*. 2014;25:497-505. 5. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214.

# Genetic Testing for AHP

- While a random (spot) urine test is the primary method to diagnose AHP, genetic testing can be used to help determine AHP type and for screening family members of patients with confirmed AHP. Not all patients with a genetic mutation for AHP develop symptomatic disease.<sup>1-3</sup>
- Genetic testing can be performed at any time to help determine AHP type
- Alnylam Pharmaceuticals sponsors no-charge, third-party genetic testing and counseling\* through the Alnylam Act<sup>®</sup> program 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<sup>®</sup>, visit: <https://www.alnylam.com/medical-professional-resources/genetic-testing-counseling/>

AHP Subtype <sup>1,2</sup>	Mutations in Genes Encoding Deficient Enzymes <sup>3,4</sup>
AIP	Hydroxymethylbilane synthase (HMBS)
HCP	COPROgen oxidase (CPOX)
VP	PROTOgen oxidase (PPOX)
ADP	ALA dehydratase (ALAD)

\*Both genetic testing and genetic counseling are available in the US and Canada

**References:** 1. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. 2. Wang B, et al. *Gastroenterology.* 2023;164(3):484-491. 3. Balwani M et al. *Hepatology.* 2017;66:1314-1322. 4. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26.

# A Summary of the Diagnostic Journey

## Patient presentation

Hallmark symptom: severe, diffuse abdominal pain (neurovisceral pain) with no fever or leukocytosis<sup>1-3</sup>

- Nausea/vomiting, limb weakness or pain, anxiety, confusion, or skin lesions on sun-exposed areas (HCP and VP primarily) can also occur<sup>3</sup>

## Patient history

### Patient characteristics

- Gender: AHP more common in females of reproductive age but can also occur in males<sup>3,4</sup>
  - In one study, 17% of men and 83% of women with AHP had AIP<sup>4</sup>
- Family history of AHP (often unknown)

### Possible precipitating factors<sup>1,3</sup>

- Women's natural hormonal cycle
- The use of certain medications
- Extreme dieting/severe restriction of calories or carbohydrates
- Other factors

## Testing options

- PBG/delta-ALA/porphyrins random (spot) urine test<sup>1,2</sup>
  - Urine porphyrins is a nonspecific test and should not be used alone to test for AHP<sup>2</sup>
- During most acute episodes of AIP, PBG is substantially elevated<sup>2</sup>
- DNA testing can also be performed to identify the type of AHP<sup>1</sup>
- An ALA random (spot) urine test can help confirm ALAD-deficiency porphyria (ADP), an extremely rare type of AHP<sup>3</sup>

**References:** 1. Balwani M et al. *Hepatology*. 2017;66:1314-1322. 2. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 3. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. 4. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 5. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26.

# 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<sup>1</sup>
- Recognizing a cluster of signs and symptoms as well as healthcare utilization patterns can raise suspicion of AHP<sup>1,2</sup>

## The importance of prompt diagnosis

- Prompt diagnosis during acute attacks of AHP may spare patients multiple hospitalizations and unnecessary surgeries<sup>1,3,4</sup>
- Diagnosis of AHP can be delayed for up to 15 years<sup>3</sup>

## Biochemical test

- The prompt use of a random (spot) urine test for delta-ALA/PBG/porphyrins is the primary method to inform a diagnosis of AHP<sup>1,5</sup>
- Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP<sup>4</sup>
- In the 3 most common types of AHP, attacks are accompanied by a substantial increase in PBG, which can be measured in urine<sup>4</sup>

**References:** 1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 2. Rudnick SR et al. ACG 2018. Poster. 3. Bonkovsky HL et al. *Am J Med.* 2014;127:1233-1241. 4. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. 5. Balwani M et al. *Hepatology.* 2017;66:1314-1322.