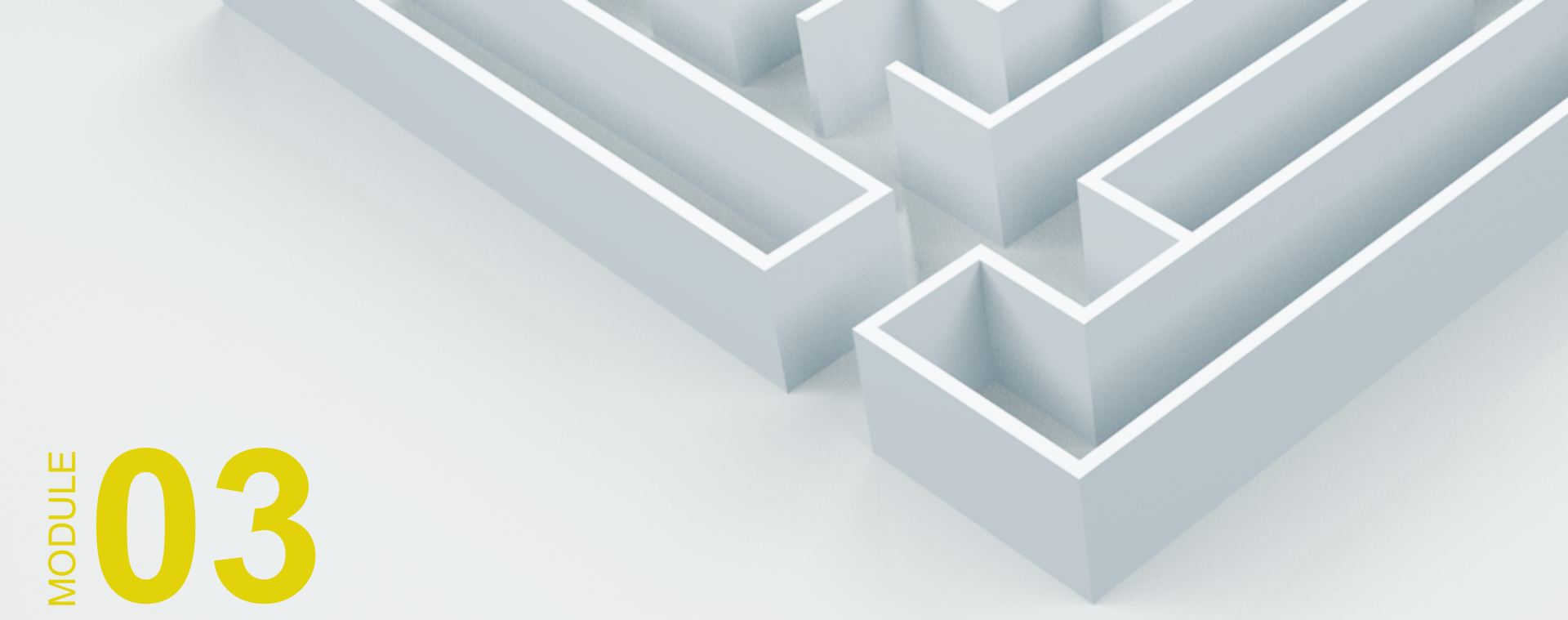


MODULE 03

Acute Hepatic Porphyria (AHP): Simplifying the Diagnostic Path

Alnylam® PHARMACEUTICALS

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

Medical zebra. The EPIC (Empowering People With Invisible Chronic Illness) Foundation website. http://www.epictogether.org/medical-zebra/. Accessed February 8, 2019.

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 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[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

1. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. **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.** Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. **6.** Rudnick SR et al. ACG 2018. Poster.

Most Common Signs and Symptoms of an Acute Attack

- Signs and symptoms of AHP* include[1-3]:

SEVERE, DIFFUSE ABDOMINAL PAIN

+

1 OR MORE OF THE FOLLOWING

PERIPHERAL Nervous System	CENTRAL Nervous System	AUTONOMIC Nervous System	CUTANEOUS†
• Limb weakness or pain	• Anxiety • Confusion	• Nausea • Vomiting	• Skin lesions on sun-exposed areas

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]

†Cutaneous symptoms occur only in HCP and VP.[1,3]

1. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. **2.** Ventura P et al. *Eur J Intern Med*. 2014;25:497-505. **3.** Balwani M et al. *Hepatology*. 2017;66:1314-1322. **4.** Simon A et al. *Patient*. 2018;11:527-537.

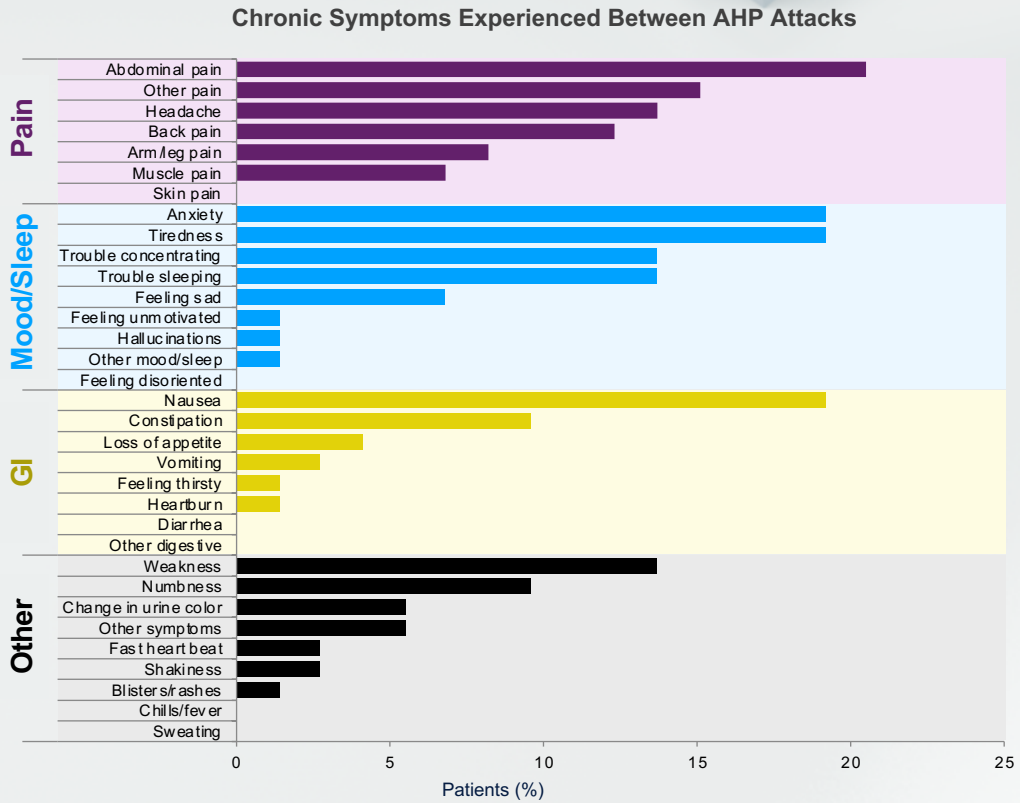
Chronic Symptoms Can Occur in Some Patients with AHP

Methods

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

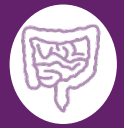
Results

- 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



Gouya L, et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 2020; May;71(5):1546-1558.

AHP Can Be Misdiagnosed as More Commonly Encountered Conditions



Other gastrointestinal disorders[1-3]

Crohn's disease
Irritable bowel syndrome (IBS)
Acute gastroenteritis with vomiting
Hepatitis

Neurological/neuropsychiatric disorders[1,3,4]

Fibromyalgia
Guillain-Barré syndrome
Psychosis

Gynecological disorders[3]

Endometriosis

Acute abdomen conditions[1,5,6]

Appendicitis
Cholecystitis
Peritonitis
Pancreatitis
Intestinal occlusion

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[1]
- Cholecystitis
- Hepatitis

Left Upper Quadrant Pain[1]
- Pancreatitis

Right Lower Quadrant Pain[1]
- Inflammatory bowel disease (IBD)
- IBS
- Appendicitis

Left Lower Quadrant Pain[1]
- IBD
- IBS

Any location[1]
- Intestinal obstruction
- Peritonitis

AHP Acute Abdominal Pain
- Severe, diffuse, unremitting abdominal pain without fever or leukocytosis[2]

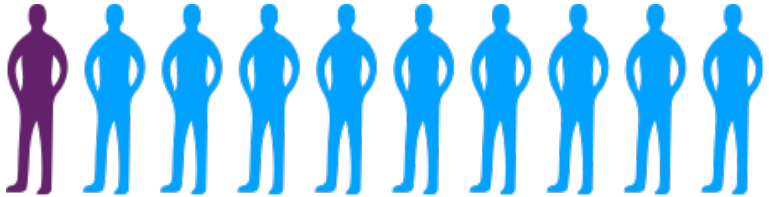
1. Cartwright SL, Knudson MP. *Am Fam Physician*. 2008;77:971-978. **2.** Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

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 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.

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

Common Features of AHP Patients

Demographics

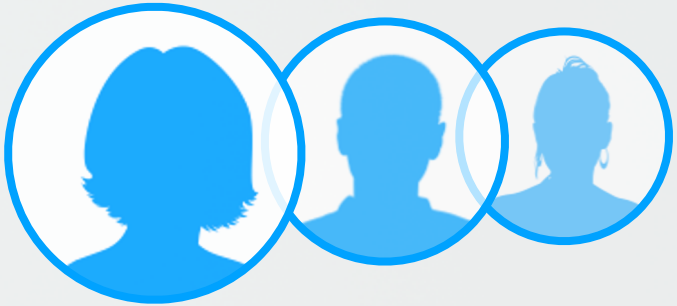
- AHP occurs most frequently in women of reproductive age[1]
  - Rare for signs and symptoms to occur before puberty[1], although diagnosis can be delayed until after reproductive age
- AHP can occur in men as well as women[2,3]
  - In one study, 17% of men and 83% of women had AIP[2]
- AHP can occur 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 attacks

- 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]



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. Gouya L, et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 2020; May;71(5):1546-1558.
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

Online resource for clinicians

- The Drug Database for Acute Porphyria: http://www.drugs-porphyria.org/ *

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: The website allows categorisation of medicines based on what is known of their porphyrinogenic potential:

- Not porphyrinogenic (NP)
- Probably not porphyrinogenic (PNP)
- Possibly porphyrinogenic (PSP)
- Probably porphyrinogenic (PRP)
- Porphyrinogenic (P)
- Not yet classified (NC).

*The link to this website is provided as a reference for our visitors. Alnylam Pharmaceuticals does not endorse and is not responsible for the content on sites that are not owned and operated by Alnylam Pharmaceuticals.

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

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.

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), attacks 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 attacks[3-5]

Spot Urine Test	Laboratory Values by AHP Subtypes During Attack[1,6]			
	Acute Intermittent Porphyria (AIP)	Hereditary Copro-porphyria (HCP)	Variegate Porphyria (VP)	ALA Dehydratase-Deficiency Porphyria (ADP)
PBG	Increased	Increased	Increased	No increase
Delta-ALA	Increased	Increased	Increased	Increased
Porphyrins	Increased uroporphyrin	Increased copro-porphyrin (COPRO)	Increased COPRO	Increased COPRO

1. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. **2.** Balwani M et al. *Hepatology*. 2017;66:1314-1322. **3.** Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.
4. Gouya L, et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 2020; May;71(5):1546-1558.
5. Marsden JT, Rees DC. *J Clin Pathol*. 2014;67:60-65. **6**. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214.

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]

AHP Subtype[1,2]	Mutations in Genes Encoding Deficient Enzymes[1,2]
AIP	Hydroxymethylbilane synthase (HMBS)
HCP	COPROgen oxidase (CPOX)
VP	PROTOgen oxidase (PPOX)
ADP	ALA dehydratase (ALAD)

1. Balwani M et al. *Hepatology*. 2017;66:1314-1322. **2.** Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

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 leukocytosis[1-3]

- Nausea/vomiting, limb weakness or pain, anxiety, confusion, or skin lesions on sun-exposed areas (HCP and VP only) can also occur[3]

Patient history

Patient characteristics

- Gender: AHP more common in females of reproductive age but can also occur in males[3,4]
  - In one study, 17% of men and 83% of women had AIP[4]
- Race: AHP most common in Caucasians, especially northern Europeans, but can occur in all races[2,4,5]

Possible precipitating factors[1,3]

- 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 test[1,2]
  - Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP[2]
- DNA testing for diagnostic confirmation and identification of AHP subtype[1]

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[1]
- Recognizing a cluster of signs and symptoms as well as healthcare utilization patterns should raise suspicion of AHP[1,2]

The importance of prompt diagnosis

- Prompt diagnosis during acute attacks of AHP may spare patients multiple hospitalizations and unnecessary surgeries[1,3,4]

Simple biochemical diagnostic test

- The prompt use of a simple spot urine test for delta-ALA/PBG/porphyrins facilitates the differential diagnosis of AHP[1,5]
- Urine porphyrins is a nonspecific test and should not be used alone to diagnose AHP[4]
- In the 3 most common subtypes of AHP, attacks are accompanied by a clear increase in PBG, which can conveniently be measured in urine[4]

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.