

**The Education, Scholarships, Apprenticeships and Youth Entrepreneurship  
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# **The importance of prompt diagnosis in acute porphyria**

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**Cooperation strategy for knowledge transfer, internationalization and curricula  
innovation in the field of research education at the 3rd level of study – AURORA**

# Acute Hepatic Porphryia

## Unpredictable Nature of AHP Places Burden on Patients

- Patients are frequently misdiagnosed (e.g., non-specific abdominal pain, fibromyalgia, depression, endometriosis) and undergo potentially unnecessary surgeries (e.g., cholecystectomy, appendectomy, hysterectomy)<sup>1,2,5</sup>
- Frequent healthcare utilization, reduced quality of life, and reduced employment all contribute to disease burden<sup>3,4</sup>
- Unpredictable nature of attacks is a source of fear and anxiety for patients

### Illustrative Patient Experience with AHP



- In the words of patients<sup>6</sup>

“On a personal level, if I have anything planned, then it’s ruined. If you have a trip coming up or a concert or anything, you lose it.”

-AHP Patient

“Before my first porphyria attack...I was active, dynamic, and cheerful...And now, after the porphyria attack, the various attacks...I have unfortunately become tired, scared and lost.”

-AHP Patient

## AHP Disease Burden

AHP is a group of rare genetic diseases characterized by acute, potentially life-threatening attacks and, for some patients, chronic debilitating symptoms that negatively impact patients' QOL

### Disease presentation



AHP results from genetic defects leading to deficiencies in enzymes of the heme biosynthesis pathway in the liver. Although AHP-related genetic mutations are relatively common, penetrance of the disease is low.



Attacks are associated with widespread dysfunction across the autonomic, central, and peripheral nervous systems.

### Disease prognosis



Patients with AHP are at increased risk for developing numerous, multi-system (liver, kidney, circulatory, and neurologic), long-term complications and comorbidities.

### Disease burden



Due to serious non-specific symptoms, low disease awareness, a lack of knowledge regarding the correct testing procedures, and a low index of suspicion, diagnosis of AHP is often delayed for many years.



Delays in diagnosis can result in a higher burden of disease, which may include unnecessary surgeries, medical complications, paralysis, or be fatal, and long-term complications and comorbidities such as hypertension, CKD, or HCC.



Attacks often require frequent ER visits and prolonged hospitalizations / rehabilitation for disease management and may be life-threatening.



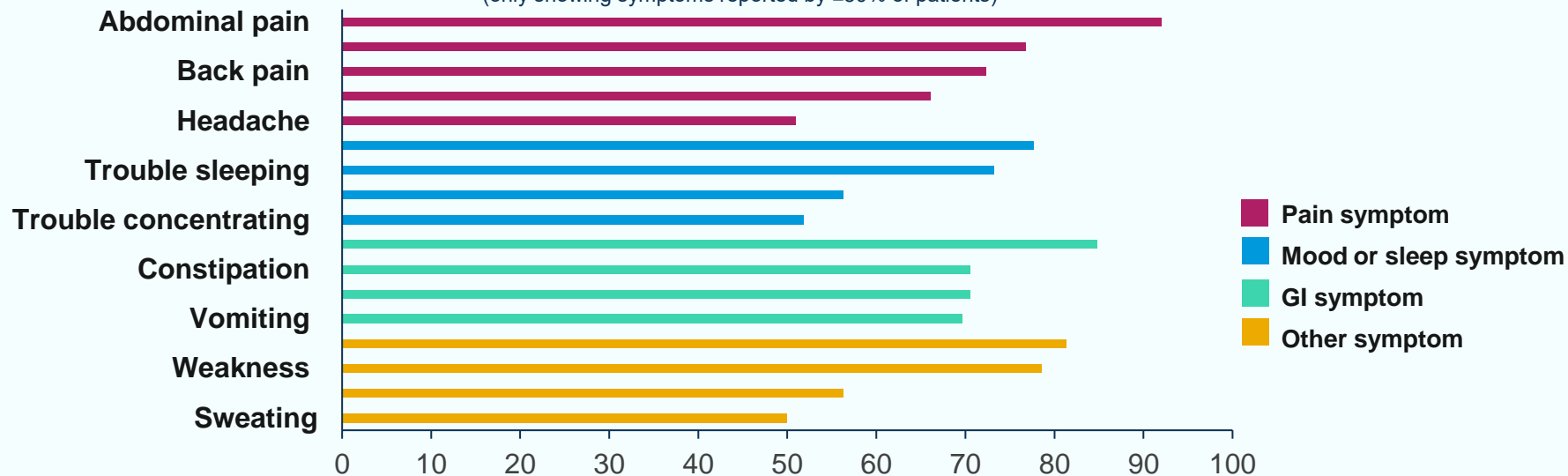
Some patients experience chronic debilitating symptoms that negatively impact physical and mental functioning, activities of daily living, work/school, and social life.

# Attack Symptomatology of AHP

## EXPLORE Study in Patients with AHP Experiencing Recurrent Attacks

### Patient-Reported Symptoms During an Attack (n=112)<sup>1</sup>

(only showing symptoms reported by ≥50% of patients)

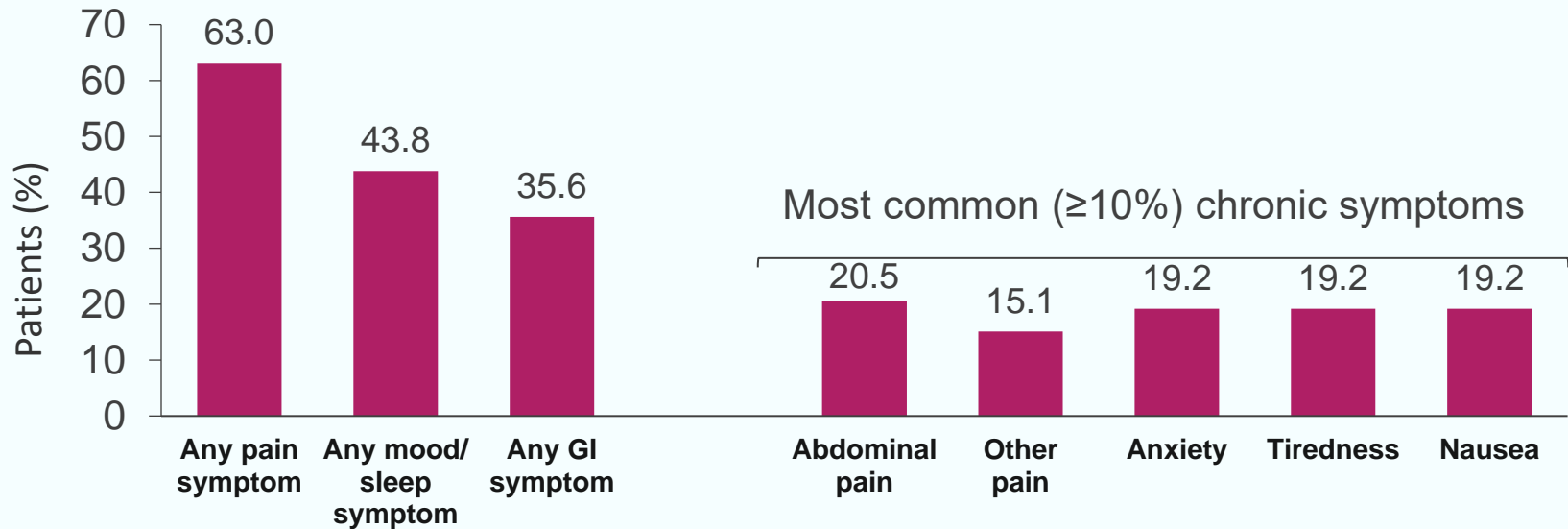


- In EXPLORE, pain was the most prominent symptom experienced during attacks
  - Abdominal pain was most common (92%), and pain in the arm/leg, back, muscles, and headache was reported by over 50% of patients
- Other common attack symptoms reported by patients included tiredness, nausea, constipation, change in urine color, and weakness<sup>1-3</sup>

# Chronic Symptoms in AHP

## EXPLORE Study in Patients with AHP Experiencing Recurrent Attacks

- Chronic symptoms between attacks were reported by 65% (n=73) of all patients (n=112)
  - Among patients experiencing chronic symptoms, 71% (n=52) reported having chronic symptoms daily<sup>1</sup>
  - Among patients experiencing chronic symptoms, 63% (n=46) reported any pain symptom<sup>2</sup>



Chronic symptoms are those occurring during asymptomatic periods

1. Gouya et al. Presented at the International Liver Congress, April 2018; 2. Ventura et al. Presented at the International Liver Congress, April 2019

# AHP patients suffer from severe long-term complications

Peripheral neuropathy (43%), systemic arterial hypertension (43%) and chronic kidney disease (29%) were the most common chronic medical conditions reported in subjects with acute intermittent porphyria.<sup>8</sup>



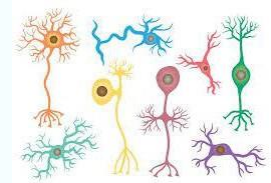
- AHP has been identified as a risk factor for primary liver cancer (PLC), especially hepatocellular carcinoma<sup>1</sup>
  - In a population-based study, the annual incidence of PLC was **0.35%** in individuals **with AHP or 108-fold higher compared with 0.003%** in the **reference population**<sup>2</sup>



- Studies have found high levels of chronic kidney disease in patients with AHP<sup>3</sup>
  - **59%** of patients with symptomatic AIP have been observed to have chronic kidney disease (eGFR <60 mL/min/1.73 m<sup>2</sup>)<sup>4</sup>



- Patients with AHP may have an increased risk of chronic sustained hypertension<sup>3,5,6</sup>
  - **>70%** of AHP patients had chronic sustained hypertension<sup>7</sup>

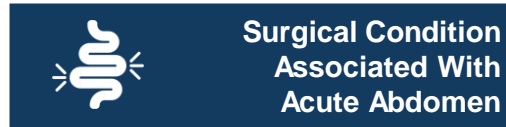


- Patients with AHP can develop chronic pain associated with axonal motor polyneuropathy<sup>6</sup>
- Chronic pain symptoms can lead to **severe depression and anxiety** which may necessitate psychiatric care<sup>6</sup>
- **>80%** of AHP patients with recurrent attacks reported **psychiatric symptoms**, with nearly 20% of patients reporting suicidality<sup>7</sup>

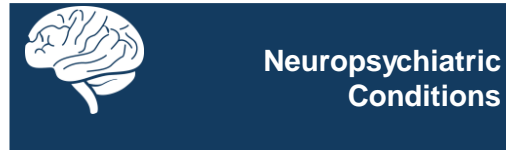
AHP, acute hepatic porphyria; eGFR, estimated glomerular filtration rate; PLC, primary liver cancer.

1. Peoc'h et al. Mol Genet Metab. 2018;S1096-7192(18)30482-7. 2. Baravelli et al. J Intern Med. 2017;282:229-40. 3. Pallet et al. Clin Kidney J. 2018;11:191-7. 4. Pallet et al. Kidney Int. 2015;88:386-95. 5. Stewart. J Clin Pathol. 2012;65:976-80. 6. Wang et al. Hepatol Commun. 2019;3:193-206. 7. Neeleman RA, Wagenmakers MAEM, Koole-Lesuis RH, et al. J Inherit Metab Dis. 2018;41(5):809-817. 8. Bonkovsky et al. Am J Med 2014;127:1233-41.

# AHP is often misdiagnosed due to the nonspecific nature of the presenting symptoms



- Peritonitis
- Appendicitis
- Acute cholecystitis
- Pancreatitis
- Intestinal occlusion



- Guillain-Barré syndrome
- Migraine
- Acute psychotic attack
- Delirium
- Acute panic attack
- Epilepsy
- Acute myopathies



- Hypertensive crisis
- Tachyarrhythmia



- Acute hemolytic crisis
- Sickle cell crisis



- Acute gastroenteritis with vomiting
- Acute pancreatitis
- Appendicitis
- Endometriosis<sup>3</sup>
- Irritable bowel syndrome<sup>3</sup>
- Pelvic inflammatory disease<sup>2</sup>

# Management Approaches for AHP

Focus on avoidance of attack triggers, treatment of acute attacks, and management of pain and other chronic symptoms<sup>1</sup>

## Hemin<sup>1,2</sup>

PANHEMATIN® (hemin for injection) is approved for the amelioration of recurrent AIP attacks<sup>3</sup> and is also used prophylactically<sup>1</sup>

## Pain medications<sup>2</sup>

Patients with AHP are commonly prescribed opioid and non-opioid pain medications

## Liver transplantation<sup>2</sup>

Liver transplantation is rarely used but due to associated complications is only suitable for severely affected patients

## Glucose and carbohydrate loading<sup>2</sup>

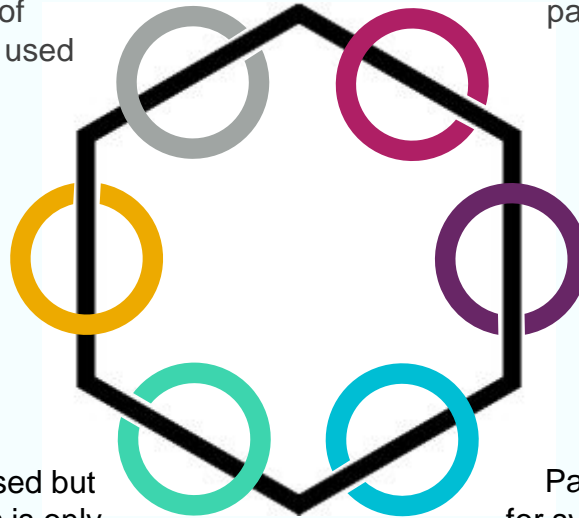
May downregulate the heme biosynthesis pathway and may be most effective in patients who are malnourished or where dietary restrictions have contributed to an attack<sup>4</sup>

## Hormone therapy<sup>2</sup>

GnRH agonists may be used chronically for women experiencing an acute attack related to their menstrual cycles

## Treatment of AHP symptoms<sup>2</sup>

Patients with AHP often receive medications for symptoms including but not limited to, nausea, hypertensive crises, neuropathy, seizures, metabolic changes, anxiety, and depression



GnRH, gonadotropin-releasing hormone

1. Balwani M, et al. *Hepatology*. 2017;66(4):1314-1322. 2. Wang. Acute Hepatic Porphyrias: Review and Recent Progress. *Hepatol Commun*. 2018 Dec 20;3(2):193-206. 3. PANHEMATIN [Package Insert]. Lebanon, NJ: Recordati Rare Diseases, Inc; 2017. 4. Anderson, KE. *Mol Genet and Metab*, <https://doi.org/10.1016/j.ymgme.2019.07.002>.

# Each attack experienced by an AHP patient is potentially life-threatening.

*“AHP is life-threatening due to the possibility of paralysis and respiratory arrest during attacks”<sup>1</sup> – European Medicines Agency*

The reported mortality is  
**5%-20%**  
during an acute attack<sup>2-4</sup>

Currently, the prognosis of patients with AIP is good even in severe attacks but deaths still occur<sup>3-8</sup>

- Causes of death were electrolyte imbalance, diaphragm paresis and recurrent asystolies<sup>4</sup>, sepsis<sup>5</sup>, acute respiratory failure<sup>6,8</sup> and cardiac arrest<sup>7</sup>.
- Oftentimes late diagnosis and subsequently potential harmful mistreatment are worsening the outcome of acute attacks towards death<sup>4-8</sup>.
- Long hospital stays lead to possible hospital induced infections that can trigger another attack<sup>4,5</sup>.

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria.

1. <https://www.ema.europa.eu/en/news/first-treatment-acute-hepatic-porphyrria>. Accessed February 3, 2020. 2. Jeans Am J Med Genet 1996; 65:269–73. 3. Pischik E, Kauppinen R. Appl Clin Genet. 2015;8:201-14. 4. Bronisch et al. Ann Hematol 2019;98(12):2683-91. 5. Mutluay B et al. Arch Neuropsychiatry 2019;56:311-312. 6. Fatima S A et al. BMJ Case Rep 2020;13:e232236. 7. Nabin A et al. Kathmandu Univ Med J 2012;38(2):96-99. 8. Stein PE et al. Clinical Medicine 2012.12(3):293-4.

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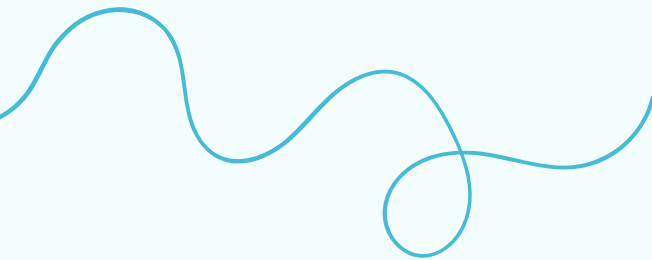
**01** About the Patient

**03** Lab tests

**02** History and physical

**04** Treatment

05



01

# Introduction of R.I.



**24 year old, Male**  
**White, Caucasian**

Without past medical history

Chief Complaint:

- Severe diffuse abdominal pain
- Weakness
- Constipation

Allergies: None

02

## History and physical

**Date:** march 2019

The patient was admitted to Regional Institute of Gastroenterology and Hepatology with *weakness, weight loss, intense abdominal pain, fever, nausea, vomiting, constipation for 3 days.*

These symptoms were interpreted as Crohn's Disease and a surgery was performed with ileocecal resection.

After several days after surgery the patient experienced *unexplained impairment of motor function.*

# A Picture Is Worth a Thousand Words



03

## Findings

### Lab tests (03/30/2019)

$\delta$ -aminolevulinic acid (ALA)

**245,48 mg/24h**

**1872,03  $\mu$ mol/24h**

(1,50 – 7,50)

(11,44 – 57,20)

Porphobilinogen (PBG)

**35,57 mg/24h**

(0,10 – 1,70)

Laboratory test (April 2019)		Result	Normal range
24h urine	Porphyrins (direct spectrometry)	4642 nmol	40 – 310
	Coproporphyrin	945 nmol	40 – 265
	Uroporphyrin	3697 nmol	1 – 45
	Porphobilinogen	570 umol	4 – 9
	Delta-aminolevulinic acid	250 umol	13 – 38
	PBG deaminase	39 nmol/g Hb	0 - 65





04

# Treatment



# Treatment

- **HUMAN HEMIN (NORMOSANG)**

4 mg/kg, daily for 4 days, infused intravenously over at least 30 min into a central vein

- **GIVOSIRAN**

Dose: 2.5 mg/kg once monthly, administered via subcutaneous injection

Total amount: 175 mg

Total volume: 0,925 ml

- **KINETOTHERAPY**



# Evolution

Improvement of  
neurological symptoms



Normal urine color



**Thank you!**

