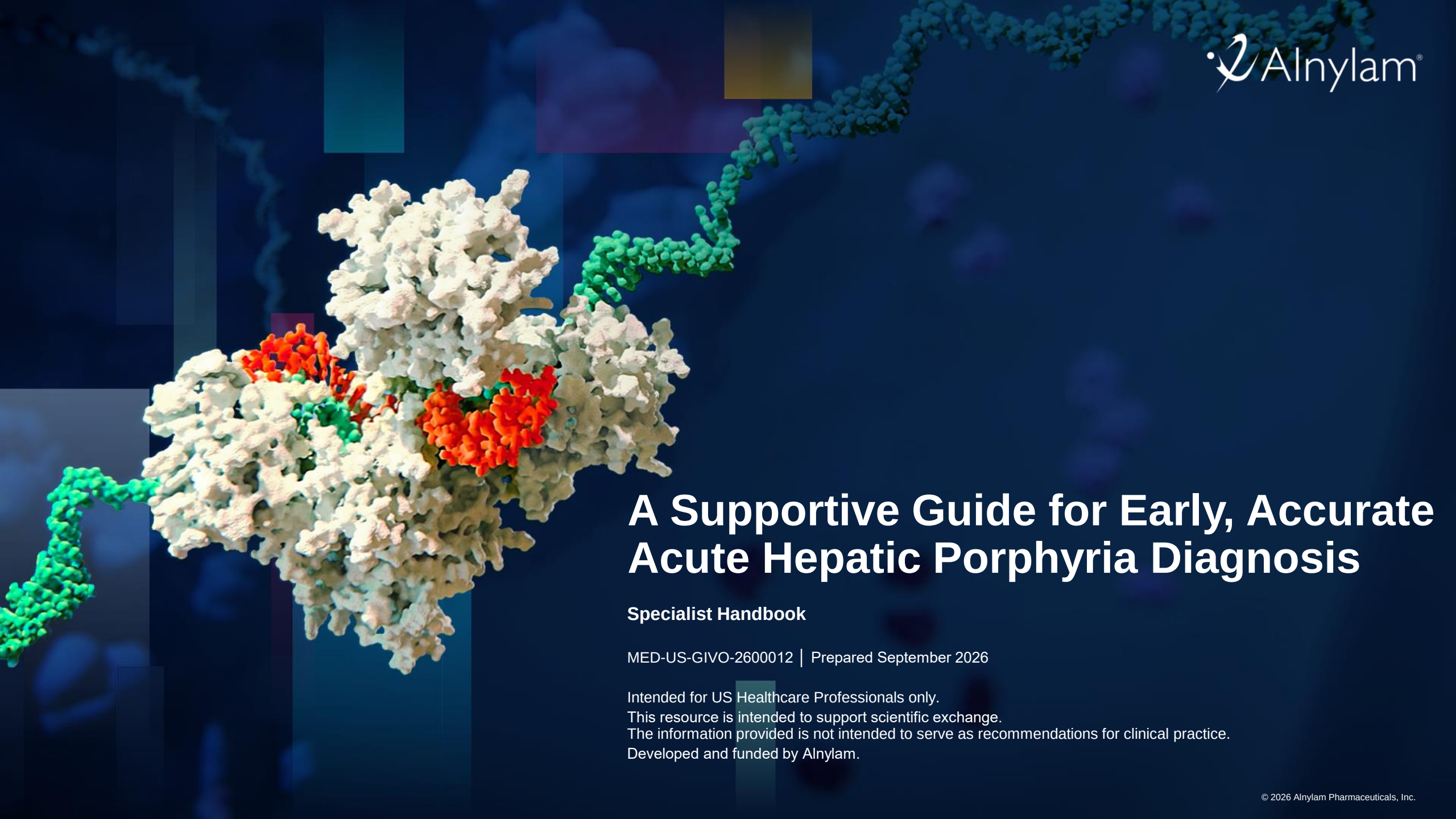


A large, detailed 3D molecular model of a protein structure, primarily white with red and green highlights, set against a dark blue background with vertical color bars and a DNA double helix.

A Supportive Guide for Early, Accurate Acute Hepatic Porphyria Diagnosis

Specialist Handbook

MED-US-GIVO-2600012 | Prepared September 2026

Intended for US Healthcare Professionals only.

This resource is intended to support scientific exchange.

The information provided is not intended to serve as recommendations for clinical practice.

Developed and funded by Alnylam.

Delayed Diagnosis and Misdiagnosis Significantly Contribute to the Burden of AHP

Intro

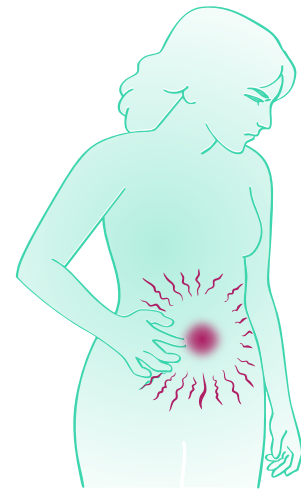


Summary

Ref & abbs

Patients with AHP may experience

- Potentially life-threatening acute neurovisceral attacks, that commonly manifest as severe abdominal pain along with other signs and symptoms^{1,2}
- Debilitating chronic symptoms (pain, fatigue, nausea, and anxiety)^{1-3,*}
- Flares in chronic baseline symptoms⁴
- Disability, diminished quality of life, and social isolation¹⁻³



Disease manifestations

Over time, patients with AHP are at risk of developing



Primary liver cancer¹



Chronic kidney disease²



Hypertension^{2,4}



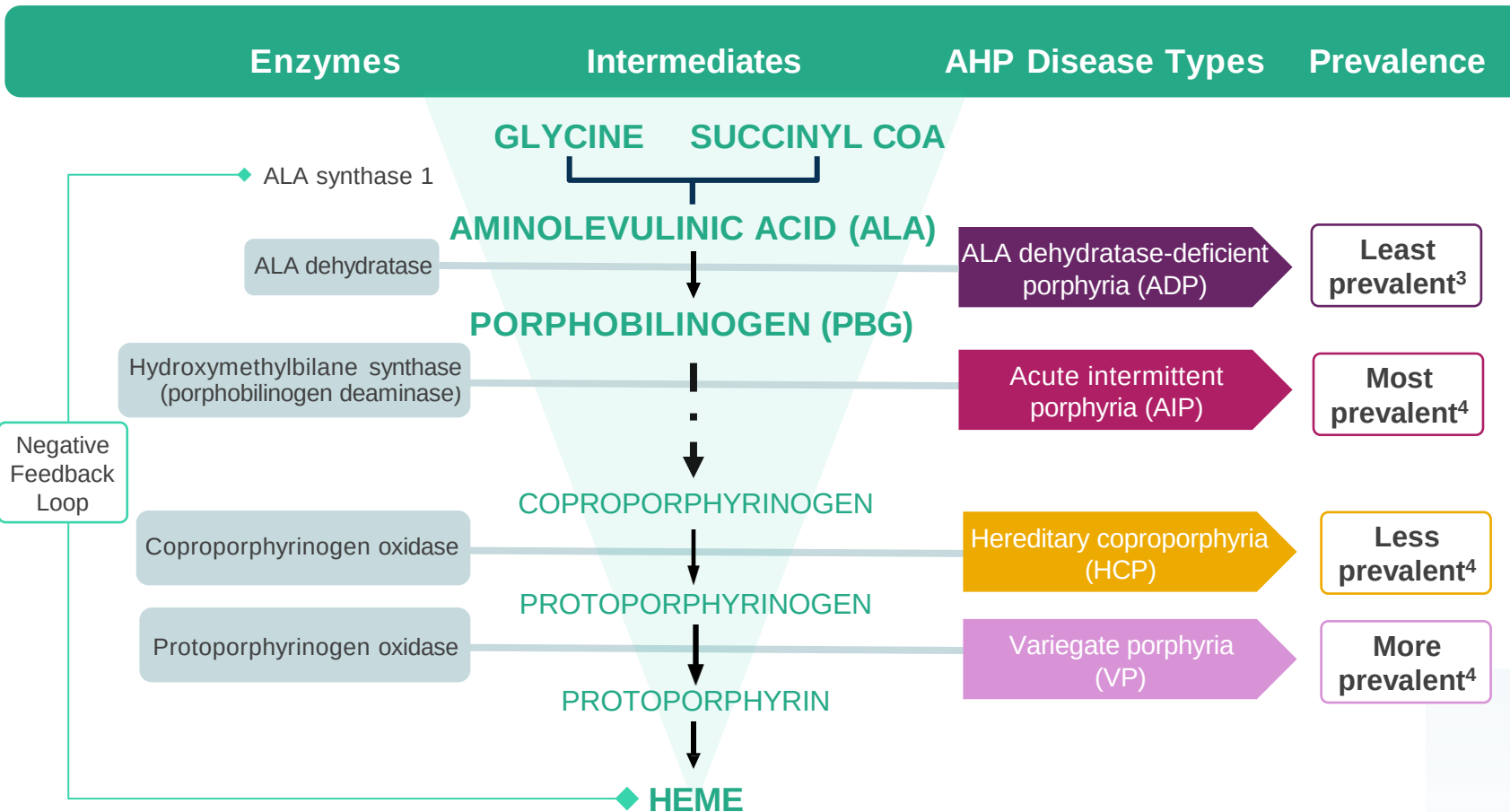
Chronic neuropathy^{5,6}



Patients with AHP often experience misdiagnosis or delayed diagnosis (≥ 15 years from initial presentation to diagnosis on average), leading to delayed access to appropriate management, which may contribute to long-term complications or potentially fatal outcomes^{1,6-9}

*These are the most commonly reported chronic symptoms (baseline results from EXPLORE A, a prospective, global, natural history study of patients [N=112] with AHP who experienced ≥3 AHP attacks in the prior 12 months or received prophylactic treatment to prevent attacks).²

AHP is a Family of Rare Genetic Diseases Caused By Defects in the Heme Biosynthesis Pathway^{1,2}



Induction of ALAS1 leads to systemic accumulation of toxic heme intermediates ALA/PBG^{2,3}

Accumulation of ALA/PBG is believed to cause disease manifestations across multiple organ systems (e.g., nervous system, skin, liver, and kidneys), which may be exacerbated by certain triggers^{2,3}



Heme Synthesis Can Be Induced Through Direct/Indirect ALAS1 Activation, Resulting in Disease Manifestations¹⁻⁶

Intro



Increased heme consumption caused by¹:

- Some drugs metabolized via CYP450*
- Infections and sulfa-containing antibiotics
- Stress



Increased ALAS1 transcription in liver caused by¹:

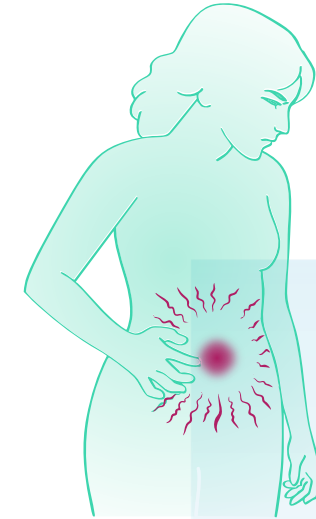
- Certain drugs and alcohol use
- Fasting/low caloric diet



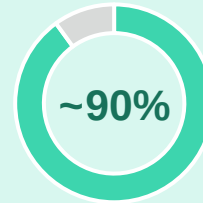
Hormonal fluctuations during menstrual cycle and pregnancy¹



Enzyme deficiency



Disease manifestations



of patients with symptomatic AHP are women and attacks are rare before onset of menses or after menopause, however AHP can also occur in men and children^{7,8}



*Examples of drugs metabolized by CYP450 with strong effects: Sulfamethoxazole-trimethoprim (CYP3A4), rifampicin (CYP2C8, CYP3A4), ciprofloxacin (CYP1A2), and fluconazole (CYP2C19). See Badia B, et al. for complete list⁹

AHP is Characterized by Chronic and Acute Symptoms¹⁻⁷

Intro



Summary

Ref & abbs

CNS Manifestations^{1,8}

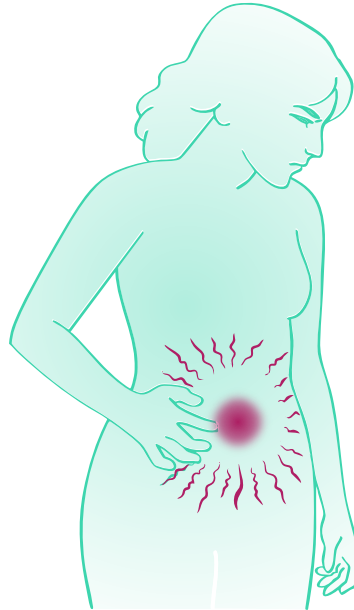
- Confusion
- Anxiety
- Memory loss
- Depression
- Tiredness
- Hallucinations*
- Seizures*

Cutaneous Manifestations^{†,8}

- Lesions on sun-exposed skin

PNS Manifestations^{1,8}

- **Neuropathic pain**
- Sensory loss
- Muscle weakness
- Paralysis*
- Respiratory failure*



Long-term Complications⁸

- Primary liver disease
- CKD
- Neuropathy
- Hypertension

ANS Manifestations^{1,8}

- **Severe pain in the abdomen, chest, or back**
- Hypertension
- Tachycardia
- **Nausea, vomiting**
- Constipation
- Hyponatremia

Common misdiagnoses

include non-specific abdominal pain, fibromyalgia, depression, endometriosis, and IBS^{9,10}

This is not a comprehensive list of all signs or symptoms of AHP

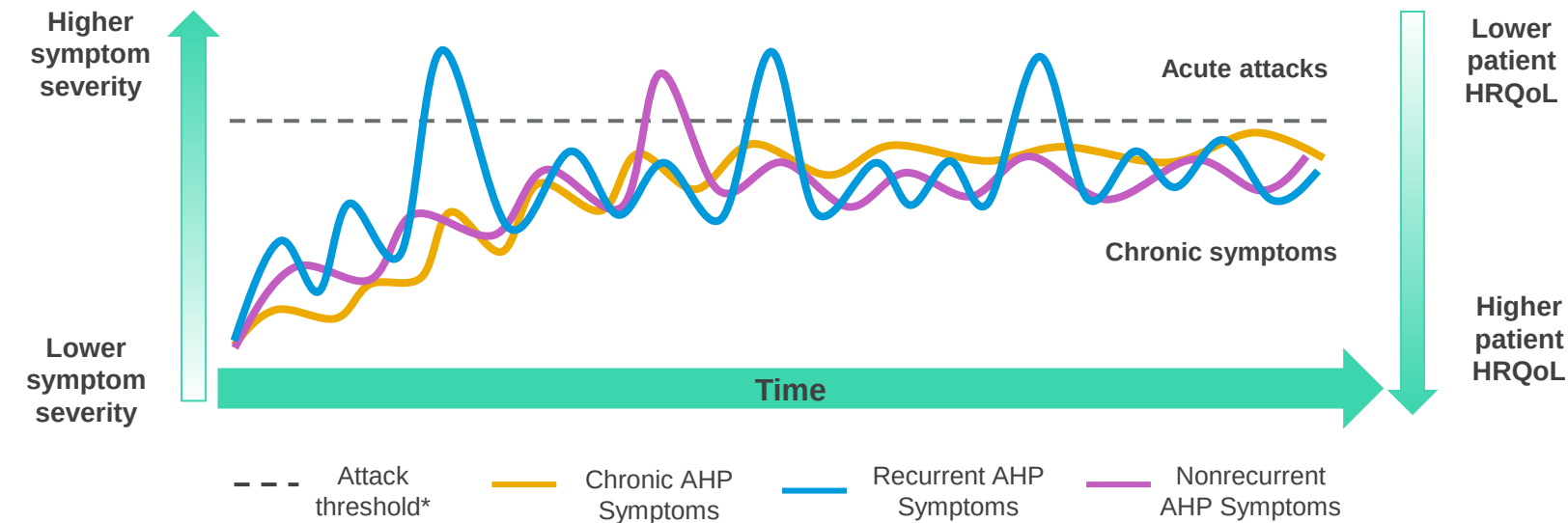
Bolding represent key symptoms.

**Only occurs in severe cases.⁸ †Only occurs in VP and HCP.⁸*

AHP Affects HRQoL Regardless of Attack Frequency

Intro

Hypothetical AHP patient archetypes¹⁻⁶



Graph shown reflects hypothetical archetypes based on expert HCP experience along with published scientific literature

Patients with AHP experience ongoing disease burden which negatively impacts their QoL^{3,7}

Patients may experience prolonged periods of **chronic symptoms, flares in chronic symptoms, and acute attacks** without appropriate management^{2,3}

Over time patients may **adapt their daily activities to accommodate chronic symptoms**³

Information regarding disease activity and clinical management of affected patients may provide a better understanding of disease manifestations²

^{*}Typically defined as requiring hospitalization or healthcare facility intervention.²

AHP is a Systemic Condition that Shares Symptomology with Other Conditions Across Multiple Clinical Specialties

Intro



Neurology /
Pain department



Psychiatry



Gastroenterology



Emergency department



Nephrology



Pediatrics



Metabolic/endocrinology/
hematology



Gynecology



Click on the specialty to find out more about symptoms that may be indicative of AHP and common conditions where a high suspicion of AHP is warranted

Summary

Ref &
abbs

AHP Considerations for Neurologists and Pain Specialists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Neurologists / Pain Specialists

Patients with AHP frequently present to neurologists because symptoms can mimic GBS, PRES, epilepsy, or acute myopathy¹⁻³



- Atypical clinical markers such as **abdominal pain, hyponatremia, autonomic dysfunction, and dark urine** are clues indicative of AHP^{1,2}
- Early **ALA/PBG testing** is essential in patients presenting with symptoms that are GBS-like, PRES-like, or in cases of unexplained seizures^{1,2}
 - Note: A diagnosis of AHP does not exclude the presence of other concomitant neurological conditions^{4,5}



11% of patients admitted to neurological wards with acute polyneuropathy or encephalopathy with abdominal pain, back pain and/or dysautonomia had AIP*,²



*Based on data from a study investigating the frequency of acute porphyria among 108 patients admitted to a neurological ward.²



Neurological/Pain Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro



Summary

Ref & abbs

SYMPTOMS¹⁻⁶



Mood or sleep symptoms

- Tiredness
- Trouble sleeping
- Anxiety
- Trouble concentrating
- Feeling unmotivated*



Hallucinations



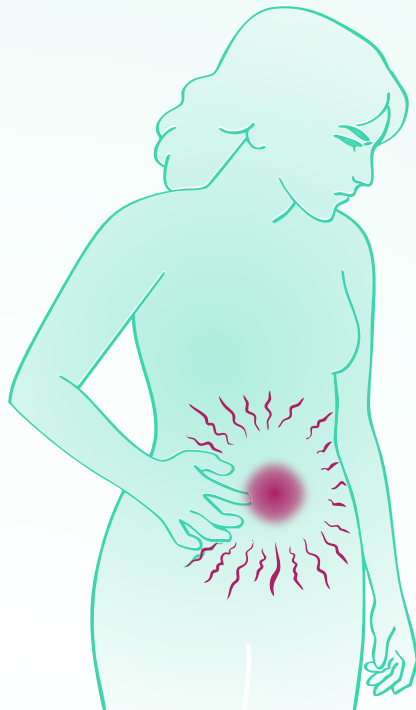
Pain symptoms

- Abdominal pain
- Arm/leg pain
- Back pain
- Muscle pain
- Headache
- Lesions on sun-exposed skin
- Other pain, including allodynia



Other neurological symptoms

- Weakness
- Numbness
- Seizures
- Muscle weakness
- Neuropathic pain
- Sensory loss



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack²

CONDITIONS⁶⁻¹⁷

- Epilepsy
- PRES
- Functional neurological disorder
- Metabolic/toxic encephalopathy
- RCVS
- GBS
- Parsonage–Turner syndrome
- Demyelinating disorders
- Paresthesia
- Fibromyalgia
- Familial Mediterranean Fever

All symptoms can be both acute and chronic unless otherwise stated. *Chronic symptom only. †Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.²

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

- **Acute peripheral neuropathy and pain or dysautonomia:**^{1,2}

Any patient with an acute or subacute motor polyneuropathy in combination with moderate-to-severe abdominal or back pain and/or signs of autonomic dysfunction

- **Acute encephalopathy and pain or dysautonomia:**^{1,2}

Any patient with acute or subacute cognitive impairment (encephalopathy) with moderate-to-severe abdominal or back pain and/or autonomic dysfunction

- **Unexplained seizures and pain or dysautonomia:**^{1,2}

Patients presenting with acute onset seizures alongside severe abdominal or back pain and/or autonomic features



Neurological complications are important components of an AHP attack

Early diagnosis and appropriate management may improve prognosis and may prevent severe neurological complications^{2,3}

Consider AHP as a differential diagnosis in patients with mental status changes, seizures, GBS, PRES, dysautonomia, and motor and sensory neuropathies^{1,2}



Click for diagnostic workflow
for AHP

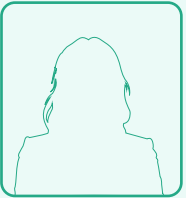
AHP Case Scenario:

Case of Peripheral Neuropathy Misdiagnosed as Parsonage-Turner Syndrome (Neuralgic Amyotrophy)

Theuriet J, Gerfaud-Valentin M, Durel CA, et al.
Neuralgic amyotrophy presentation of acute intermittent
porphyria: A case report. *J Peripher Nerv Syst.*
2024;29(4):567-569

AHP Misdiagnosed as Parsonage-Turner Syndrome

Clinical presentation and initial workup¹



Patient: 41-year-old | Female

Presented with:

- Burning pain and electric shock-like sensations in the shoulder and trunk
- Asymmetrical motor weakness in upper limbs affecting arm abduction, shoulder rotation and finger extension
- Dysesthesia
- Nerve conduction study showed decreased nerve action potential amplitude of the superior trunk and brachial plexus
- Needle electromyography showed fibrillations at rest in muscles of the shoulder, forearm and fingers
- Sympathetic skin responses and electrochemical skin conductance were abnormal in both feet

Notable medical history:

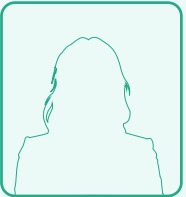
- Fibromyalgia managed with morphine for 5 years, but stopped several months prior to current presentation
- Antiphospholipid antibody syndrome managed with vitamin K antagonist
- Reported cannabis use

Initial misdiagnosis and treatment

- **Neuralgic amyotrophy** involving the superior trunk of the brachial plexus and the posterior interosseous nerve, possibly associated with small fiber neuropathy
- Symptoms improved initially, but 14 months later she experienced an **acute relapse of symptoms with abdominal burning pain and severe constipation**

AHP Misdiagnosed as Parsonage-Turner Syndrome

Additional clinical investigation¹



Patient: 41-year-old | Female

Tests conducted:

- **Nerve conduction study and needle electromyography:** further deterioration of the posterior interosseous nerve function; reappearance of fibrillations in the finger extensor muscles
- **Visual inspection:** Orange colored urine
- **Urine analysis of ALA and PBG:**

Laboratory test	Laboratory value	Result
Urine PBG	34 nmol/mol creatine (normal < 3)	Elevated
Urine ALA	97.4 nmol/mol creatine (normal < 1)	Elevated

- **Genetic testing:** heterozygous pathogenic variant in the *HMBS* gene (p.Trp198Glyfs*57)

Acute intermittent porphyria (AIP) confirmed

Patient received treatment for AIP and was followed up to monitor for further attacks

Key AIP symptoms in this patient¹

- Progressive motor weakness
- Abdominal burning pain
- Dark urine
- Severe constipation

AHP Considerations for Psychiatrists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Psychiatrists

Psychiatric syndromes are common in AIP and at times are the presenting or only manifestation¹⁻⁵



- A review encompassing 3867 patients with psychiatric conditions found AIP prevalence to be **20× higher in this cohort compared to the general population²**
- Individuals with AIP have markedly increased risks of **schizophrenia** (RR $\approx$ 3.6) and **bipolar disorder** (RR $\approx$ 3.7) compared to individuals without symptomatic AIP; first-degree relatives of individuals with AIP also had elevated risks of schizophrenia (RR $\approx$ 1.6) and bipolar disorder (RR $\approx$ 1.8)¹
- Schizophrenia spectrum disorders (SSD) are commonly associated with a range of non-psychiatric conditions of different etiologies, including neurometabolic diseases, as well as infections and endocrine-, immunological-, (para)neoplastic-, and epileptiform disorders⁶

AHP is rare⁷ but disproportionately present among patients with psychiatric conditions⁴

AHP may masquerade as primary psychiatric disease⁴



Intro



Summary

Ref &
abbs

Psychological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro



Summary

Ref & abbs

SYMPTOMS¹⁻⁴



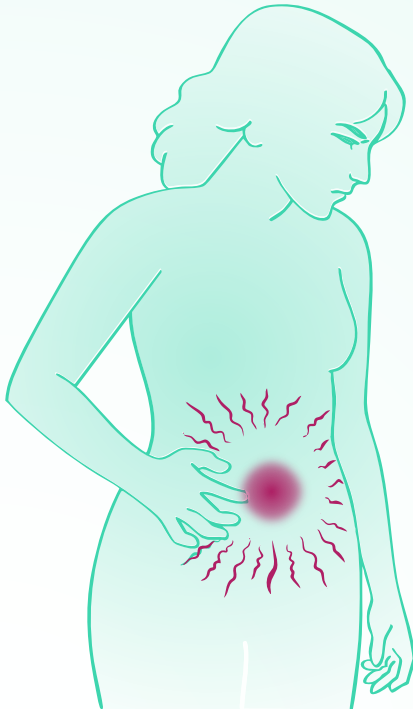
Mood or sleep symptoms

- Tiredness
- Trouble sleeping
- Anxiety
- Trouble concentrating
- Feeling unmotivated
- Depression



Other symptoms

- Hallucinations
- Delirium
- Psychosis
- Memory loss
- Confusion



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack¹

CONDITIONS⁵⁻¹⁷

- Schizoaffective disorder
- Schizophrenia
- Bipolar I disorder
- Bipolar I disorder with psychotic features
- Manic episode with psychotic features
- Brief psychotic disorder
- Psychosis due to general medical condition
- Acute psychosis
- Panic attack

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.¹

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

Porphyria testing or liaison with internal medicine is indicated when patients present with:

- **Psychosis with abdominal pain**^{1,2}
- **Atypical or treatment-resistant psychosis**, oscillating attention/orientation, fluctuating mood/behavior, or catatonic features - specially when accompanied by **intermittent abdominal pain** or other unexplained somatic complaints¹
- Personal history suggesting **gynecological/obstetric triggers (such as those around peri-menses)**^{3,4} or a family history of psychiatric illness or AHP⁵

Psychosis may be the sole clinical manifestation of AHP⁶

It is recommended that porphyria is considered as a differential diagnosis in patients with non-specific presentations, poor response to standard therapy, and co-existing somatic symptoms^{1,7}



Click for diagnostic workflow for AHP



AHP Case Scenario:

Acute psychiatric symptoms
misdiagnosed as schizoaffective
disorder

Eroglu S, Birsenogul I. Delirium With Delayed Diagnosis of Hereditary Coproporphyrria. *Clin Case Rep.* 2022;10(6):e05937

AHP Misdiagnosed as Schizoaffective Disorder

Clinical presentation and initial workup¹



Patient: 66-year-old | Male

Presented with:

- Violent behavior, restlessness, disorientation, delusions and visual hallucinations
- Mental status examination revealed labile affect, limited cognition, and poor insight and judgment
- Rapid and pressured speech
- Skin lesions on the dorsum of the hands and forearms
- Complete blood count, blood glucose, serum creatinine, liver function tests, total bilirubin, albumin, and protein levels were normal; urine toxicology screen was negative

Notable medical history:

- Dementia
- Insomnia
- Depressive disorder
- Medications: cyanocobalamin, fluoxetine, olanzapine

Initial misdiagnosis and treatment

- **Schizoaffective disorder** and received treatment of haloperidol, olanzapine, divalproex sodium, lorazepam, fluoxetine, and diphenhydramine
- **Symptoms progressively worsened** with hyperactive delirium, increasingly agitated mental state, atrial fibrillation, rapid heart rate and skin lesions on upper extremities

AHP Misdiagnosed as Schizoaffective Disorder

Additional clinical investigation¹



Patient: 66-year-old | Male

Tests conducted:

- Ischemic white matter changes were noted
- **Infectious workup:** negative
- **Urine and stool analysis:**

Laboratory test	Laboratory value	Result
Urine PBG	1.9 mg/L (normal 0.0-2.0 mg/L)	Normal
Urine ALA	Data not available	Normal
Urine Coproporphyrin I	163 µg/L (normal range 0-15 µg/L)	Elevated
Urine Coproporphyrin III	778 µg/L (normal range 0-49 µg/L)	Elevated
CIII:CI ratio	2.94 (normal range < 1.20)	Elevated

Key HCP symptoms in this patient

- Acute neuropsychiatric symptoms
- Skin lesions
- Dark urine

Hereditary coproporphryia (HCP) confirmed

The patients' ongoing medications were reviewed and adjusted to avoid porphyrinogenic drugs, and the patient was counselled on trigger avoidance

This is a real patient case. Individual experiences may vary.

AHP Considerations for Gastroenterologists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Gastroenterologists

Patients with AHP commonly present first and repeatedly in GI settings with severe recurrent abdominal pain but normal imaging and negative standard GI workups¹



- Many patients undergo **years of misdiagnosed GI symptoms**, repeated ER visits, and unnecessary surgeries before AHP is recognized^{1,2}
- Many patients with AHP undergo **unjustified surgical procedures** such as appendectomies and cholecystectomies²

GI symptoms are common manifestations of AHP and overlap with symptoms associated with functional abdominal disorders and IBS¹

A high clinical suspicion is therefore warranted to ensure timely diagnosis and appropriate intervention³



Intro



Summary

Ref &
abbs

GI Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro



Summary

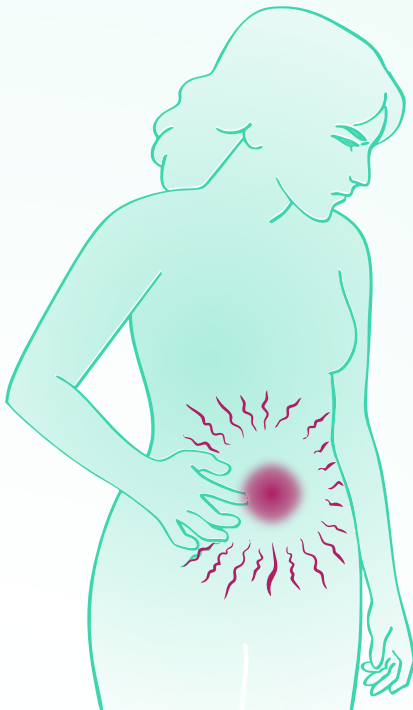
Ref &
abbs

SYMPTOMS^{1,2}



GI symptoms

- Severe diffuse abdominal pain
- Nausea
- Constipation
- Loss of appetite
- Vomiting
- Heartburn



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack²

CONDITIONS³⁻¹⁰

- Partial intestinal obstruction
- Irritable bowel syndrome
- Cholecystitis
- Viral hepatitis
- Acute gastroenteritis with vomiting
- Intestinal ischemia
- Appendicitis
- Peritonitis
- Pancreatitis

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.²

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

Patients with severe, persistent and poorly localized abdominal pain, accompanied by:¹

- **Lack of peritoneal irritation**
- **Additional pain symptoms:** lower limb pain, back pain
- **GI symptoms:** nausea, vomiting, constipation



High clinical suspicion of AHP in patients who present with red-flag symptoms may enable timely management, minimize avoidable morbidity, and reduce repeat healthcare utilization^{1,2}



Click for diagnostic workflow
for AHP

AHP Case Scenario:

GI Symptoms Misdiagnosed as Partial Intestinal Obstruction

Indika NLR, Kesavan T, Dilanthi HW, et al. Many Pitfalls in Diagnosis of Acute Intermittent Porphyrria: A Case Report. *BMC Res Notes*. 2018;11(1):552.

AHP Misdiagnosed as Partial Intestinal Obstruction

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Presented with:

- Recurrent episodes of severe abdominal pain, nausea, vomiting, constipation
- Numbness of bilateral lower limb extremities

Notable medical history:

- Five hospital admissions due to neurovisceral attacks over the past 2 years

Initial misdiagnosis and treatment

- **Appendicitis**; emergency laparoscopic exploration
- **Partial intestinal obstruction**; conservatively managed
- While awaiting diagnostic laparoscopy, the patient developed **confusion and was found to have systemic hypertension**

Intro



Summary

Ref &
abbs

AHP Misdiagnosed as Partial Intestinal Obstruction

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Tests conducted:

- Watson and Schwartz test for urine PBG: positive
- Urine analysis:

Laboratory test	Laboratory value	Result
Total porphyrin level	5505.5 nmol/L (normal <300 nmol/L)	Elevated

- **Genetic studies:** missense mutation, c.517C>T encoding p.R173W in the *HMBS* gene

Acute hepatic porphyria (AHP) confirmed

The patient was managed symptomatically, and counselled on triggers for AHP

Key AHP symptoms in this patient

- Confusion
- Hypertension
- Abdominal pain
- Dark urine

Intro



Summary

Ref & abbs

AHP Considerations for the Emergency Department

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for the Emergency Department

The emergency department is often the first and sometimes the only setting where patients experiencing severe acute porphyria attacks present^{1,2}



- During acute attacks, **symptoms are typically severe and levels of porphyrin precursors (ALA/PBG) are markedly elevated**, allowing for biochemical confirmation of AHP¹⁻⁴
 - An acute attack commonly presents as **intense abdominal pain**, alongside pain in the back and legs, nausea, vomiting, and constipation⁵
- The application of screening protocols is important for timely recognition and diagnosis of AHP⁶
- Patients with AIP may spend large amounts of time in the medical system, including multiple visits to the emergency department and/or hospitalizations⁷

Early recognition and testing for AHP in the ED is essential as untreated attacks can rapidly become life-threatening^{1,2}

Simple biochemical screening tests can help identify AHP early if considered as a differential diagnosis^{6,8,9}



Intro



Summary

Ref &
abbs

Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP in the Emergency Department

Intro



Summary

Ref & abbs

SYMPTOMS^{1,2}



Mood or sleep symptoms

- Tiredness
- Anxiety



Acute abdominal pain



Mental health status

- Acute psychosis (specifically first episodes, atypical presentations, or treatment-refractory cases)
- Altered mental health status
- Hallucinations



Polyneuropathy

- Muscle weakness
- Paralysis
- Numbness
- Variable sensory impairment



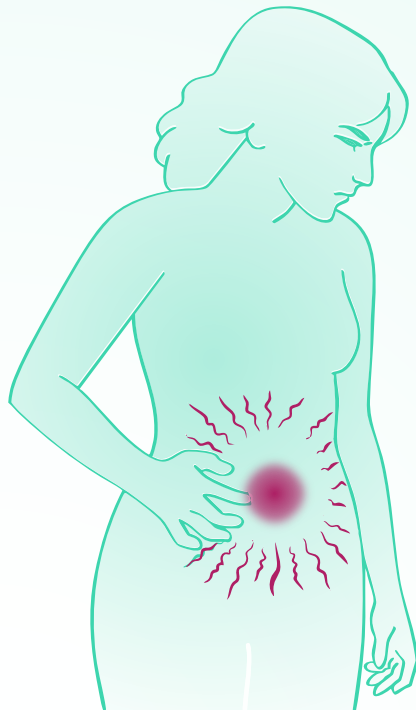
Seizures



Respiratory paralysis



Tachycardia



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack²

CONDITIONS^{1,3-5}

- Partial intestinal obstruction
- Acute pancreatitis
- Rhabdomyolysis
- Illicit substance ingestion
- Fabry disease
- Familial mediterranean fever
- Hereditary angioedema
- Cerebrovascular events
- Guillain–Barré syndrome
- Multiple sclerosis

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

Consider AHP in patients presenting with:¹

- Arterial hypertension
- Tachycardia
- Hyponatremia
- Neuropsychiatric symptoms
- Seizures
- Brown-reddish urine
- Previous episodes of abdominal pain of unclear origin
- Acute flaccid paralysis
- Acute psychosis (first episode, treatment resistant, atypical)
- Abdominal pain



Patients with AIP may spend large amounts of time in the medical system, including multiple visits to the ED and/or hospitalizations²



Click for diagnostic workflow
for AHP

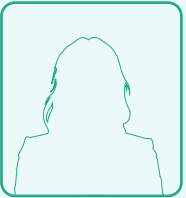
AIP Case Scenario:

Differential diagnoses of acute pancreatitis, acute kidney injury, rhabdomyolysis

Norman J, Soliman M. Unraveling Complexity: Acute Intermittent Porphyria Complicated by Rhabdomyolysis and Acute Pancreatitis. *Cureus*. 2024;16(7):e65826.

AIP Misdiagnosed as Acute Pancreatitis, Acute Kidney Injury, and Possible Rhabdomyolysis

Clinical presentation and initial workup¹



Patient: 34-year-old | Female

Presented at ED with:

- Severe abdominal pain, nausea, and oliguria
- New-onset facial numbness and weakness in her right upper and left lower extremities
- Lack of distinctive 'attack periods'

Notable medical history:

- Anxiety
- Bipolar disorder
- Reflux disease
- Deep vein thrombosis
- Prior episode of GBS

Initial misdiagnosis and treatment

- **Acute pancreatitis, acute kidney injury, and possible rhabdomyolysis** which was managed with IV fluid, pain management and antibiotics
- On Day 3 of hospitalization, **grossly dark/wine colored urine** was observed

Intro

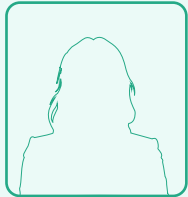


Summary

Ref &
abbs

AIP Misdiagnosed as Acute Pancreatitis, Acute Kidney Injury, and Possible Rhabdomyolysis

Additional clinical investigation¹



Patient: 34-year-old | Female

Tests conducted:

- Urine analysis (24 hours):

Laboratory test	Laboratory value	Result
Uroporphyrin I	499.3 mcg (normal 4.1-22.4 mcg/24 h)	Elevated
Uroporphyrin III	190.4 mcg (normal 0.7-7.4 mcg/24 h)	Elevated
Heptacarboxylporphyrin	55.4 mcg (normal ≤ 3.3 mcg/24 h)	Elevated
Hexacarboxylporphyrin	2.4 mcg (normal ≤ 10mcg/24 h)	Normal
Pentacarboxylporphyrin	24.4 mcg (normal ≤ 4.6 mcg/24 h)	Elevated
Coproporphyrin I	62 mcg (normal 7.1-48.7 mcg/24 h)	Elevated
Total porphyrin count	1049.3 mcg (normal 35.0-210.7 mcg/24 h)	Elevated

Acute intermittent porphyria (AIP) confirmed

The patient refused specific treatment for porphyria.

Key AIP symptoms in this patient

- Abdominal pain
- Neurological symptoms
- Dark urine

AHP Considerations for Nephrologists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Nephrologists

Intro



Summary

Ref &
abbs



Patients with AHP are at increased risk of CKD and hypertension^{1,2}

- Porphyria-associated kidney disease is associated with an annual decline in eGFR of approximately 1 ml/min per 1.73m²; among patients with PAKD, approximately 60% had concomitant hypertension¹
 - PAKD is postulated to occur due to ALA and PBG-mediated cytotoxic effects on proximal tubular cells¹
- During acute attacks systemic arterial hypertension is often observed, which can result in chronic hypertension in some patients and may be a contributing factor to progressive renal impairment^{1,2}



Chronic kidney disease is a common long-term complication of AHP^{1,3}

Ensuring control of systemic hypertension is recommended to decrease risk of CKD in patients with AHP¹

Nephrological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro

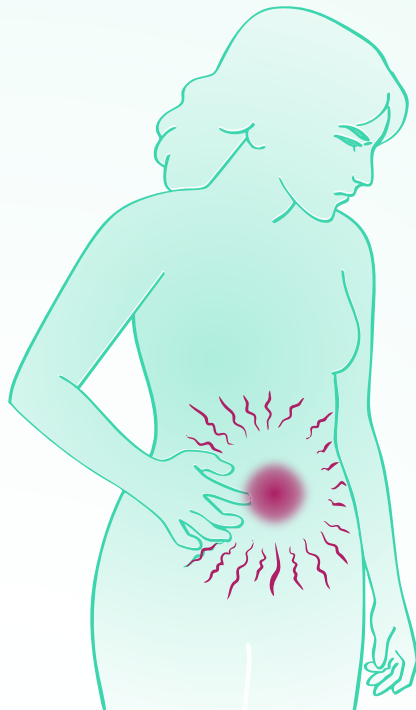


Summary

Ref & abbs

SYMPTOMS¹⁻³

CONDITIONS¹



Acute abdominal pain



Kidney symptoms

- Dark-colored urine
- Proteinuria
- Increased urinary excretion of lipoperoxides
- Impaired EPO production
- CKD



Other symptoms

- Hyponatremia
- Hypertension
- Primary liver disease

- Renal Calculi
- Drug-induced acute interstitial nephritis

This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack²

*All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.²*

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

Renal impairment has been noted in many patients with AHP, especially those who still have attacks and those who are hypertensive^{1,2}

- Porphyric patients have been reported to have signs of:³
 - Proximal tubulointerstitial insufficiency (proteinuria, impaired EPO production)
 - Oxidative damage (increased urinary excretion of lipoperoxides)



The diagnostic workup of AHPs should include a baseline evaluation of renal function and annual monitoring of the progression of kidney disease^{3,4}



Click for diagnostic workflow for AHP

AHP Case Scenario:

Misdiagnosis of Renal Calculi, and Drug-Induced Acute Interstitial Nephritis

Indika NLR, Kesavan T, Dilanthi HW, et al. Many Pitfalls in
Diagnosis of Acute Intermittent Porphyria: A Case Report.
BMC Res Notes. 2018;11(1):552.

AIP Misdiagnosed as Renal Calculi and Drug-Induced Acute Interstitial Nephritis

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Presented with:

- Neurovisceral attacks, with fever associated with the third attack, followed by a fourth attack complicated with transient hyponatremia and transiently high serum creatinine levels

Notable medical history:

- Five acute hospital admissions over two years due to neurovisceral attacks
- Medication: nonsteroidal anti-inflammatory drug twice a day for 6 weeks

Initial misdiagnosis and treatment

- **Renal colic, followed by interstitial nephritis** based on prolonged use of nonsteroidal anti-inflammatory drug
- The patient experienced **several attacks**, the last presenting with recurrent episodes of severe abdominal pain, nausea, vomiting, constipation, and numbness of bilateral lower limb extremities

AIP Misdiagnosed as Renal Calculi and Drug-Induced Acute Interstitial Nephritis

Additional clinical investigation¹



Patient: 33-year-old | Male

Tests conducted:

- Watson and Schwartz test for urine PBG: positive
- Urine analysis:

Laboratory test	Laboratory value	Result
Total porphyrin level	5505.5 nmol/L (normal <300 nmol/L)	Elevated

- **Genetic studies:** missense mutation, c.517C>T encoding p.R173W in the *HMBS* gene

Acute hepatic porphyria (AHP) confirmed

The patient was managed symptomatically, and counselled on triggers for AHP

Key AHP symptoms in this patient

- Confusion
- Hypertension
- Abdominal pain
- Dark urine

AHP Considerations for Pediatricians

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Pediatricians

AHP most commonly present in women aged 15-50 years, but it can present in men and women at any age¹⁻⁴



- Although rare, published cases of AHP manifesting in **infants, children and adolescence** highlight the importance of considering this diagnosis in the pediatric setting²⁻⁴
- **Hormonal changes during adolescence** including dramatic changes in liver metabolism, or initiation of the menstrual cycle can trigger attacks²
- **Family screening and genetic counseling** is warranted to inform of risks of acute attacks among family members¹



AHP typically presents in adults and may therefore be under-recognized in pediatric populations³

High clinical suspicion is required for early recognition and appropriate intervention³

Intro



Summary

Ref &
abbs

Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP in Pediatric Populations

Intro



Summary

Ref & abbs

SYMPTOMS¹⁻⁸



Mood or sleep symptoms

- Tiredness
- Anxiety



Mental health status

- Acute psychosis (specifically first episodes, atypical presentations, or treatment-refractory cases)
- Mental confusion



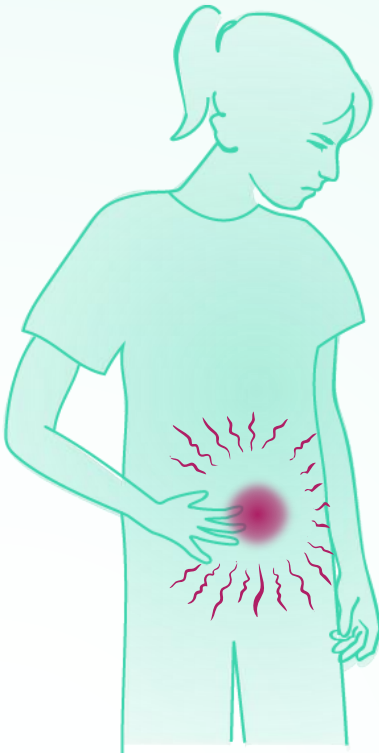
Unexplained acute abdominal pain

- Vomiting
- Nausea



Other neurological symptoms

- Acute or subacute polyneuropathy
- Seizures
- Respiratory paralysis
- Tachycardia
- Muscle weakness
- Difficulty standing



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack⁷

CONDITIONS¹⁻⁶

- Partial intestinal obstruction
- Acute pancreatitis
- Cerebrovascular events
- Illicit substance ingestion
- Pediatric onset of seizures
- Appendicitis
- Viral gastroenteritis
- Prader-Willi syndrome
- Myotonic dystrophy
- Spinal muscular atrophy syndrome

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.⁷

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

Unexplained neurovisceral or phototoxic symptoms should cause suspicion of AHP in pediatric patients and trigger proactive biochemical testing^{1,2}

- Pink/red colored urine or staining of the diaper may be indicative of AHP
- AHP should also be considered in patients with psychiatric and neurological manifestations, especially in the context of first presentation, atypical presentation or treatment-refractory cases



Medical history may reveal family members with previous symptomatic disease; however, this may be in the absence of an associated AHP diagnosis¹

Due to the overall **low penetrance of pathogenic disease**, a history of symptomatic family members may not be present¹



Click for diagnostic workflow
for AHP

AHP Case Scenario:

Neuropsychiatric Symptoms of New Onset Seizures/Encephalopathy in Diagnostic Journey of AHP

Dukkipati SS, Terschluse J, Thodeson D, et al. Porphyric Encephalopathy in a 15-Year-Old Girl: A Case Report. *SAGE Open Med Case Rep.* 2025;13:2050313X241298532.

New-Onset Seizures/Encephalopathy in the Diagnostic Journey of AHP

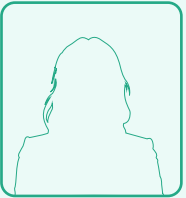
Clinical presentation and initial workup¹

Intro



Summary

Ref &
abbs



Patient: 15-year-old | Female

Presented with:

- New-onset tonic-clonic seizures, confusion, unresponsiveness with stiffening of her extremities
- Diffuse sharp abdominal pain, hypertension, hyponatremia, emaciation, anxiousness, vomiting and minimal oral intake
- Brain MRI showing bilateral relatively symmetric areas of cortical signal within the frontal, parietal, and occipital lobes

Notable medical history:

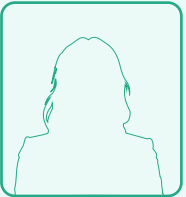
- Recreational cannabis and nicotine use
- Weight loss

Diagnostic journey and initial management

- **Encephalitis** treated with corticosteroids, IV immunoglobulin, and anti-hypertensive drugs
- **Cannabis hyperemesis syndrome** treated with analgesic medication and serotonin antagonist on parenteral nutrition until abdominal pain and emesis improved
- **SIADH** treated with fluid restriction
- **Dark urine** was observed on Day 5 of hospitalization, along **abdominal pain and neuropsychiatric symptoms**

New-Onset Seizures/Encephalopathy in the Diagnostic Journey of AHP

Additional clinical investigation¹



Patient: 15-year-old | Female

Tests conducted:

• Urine analysis:

Laboratory test	Laboratory value	Result
Random PBG	314.5 µmol/L (normal <9 µmol/L)	Elevated
Uroporphyrin	87 µmol/molCRT (normal 0–4 µmol/molCRT)	Elevated
Heptacarboxylate	6 µmol/molCRT (normal 0–2 µmol/molCRT)	Elevated
Coproporphyrin I	10 µmol/molCRT (normal <30 nmol/molCRT)	Elevated
Coproporphyrin II	83 µmol/molCRT (normal <30 nmol/molCRT)	Elevated
ALA	158 µmol/L (normal 0–35 µmol/L)	Elevated

• Genetic testing: *HMBS* (C.510_511del, p.Asn173Hisfs*38) pathogenic variant

Key AIP symptoms in this patient

- Hypertension
- Abdominal pain
- Dark urine

Acute intermittent porphyria (AIP) confirmed

The patient was managed symptomatically and received multidisciplinary follow-up for management of AIP

This is a real patient case. Individual experiences may vary.

AHP Considerations for Endocrinologists, Metabolic Specialists, and Hematologists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Endocrinologist/Metabolic Specialists and Hematologists

AHP is a rare genetic disease caused by deficiency in the heme biosynthesis pathway^{1,2}

- Known triggers for AHP attacks include:
 - Hormonal changes during adolescence³
 - Physiological fluctuations during the menstrual cycle⁴
 - Rapid weight loss⁵
 - Carbohydrate restricted diets⁵

Consider AHP in patients with unexplained hyponatremia, cyclical or hormonally linked symptoms, metabolic disturbances, or hematologic abnormalities¹⁻⁶

Intro



Summary

Ref &
abbs



Endocrine/Metabolic/Hematological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro



Summary

Ref & abbs

SYMPTOMS¹⁻⁵



GI symptoms

- Nausea
- Vomiting
- Abdominal pain
- Constipation



Mood or sleep symptoms

- Tiredness
- Mood changes



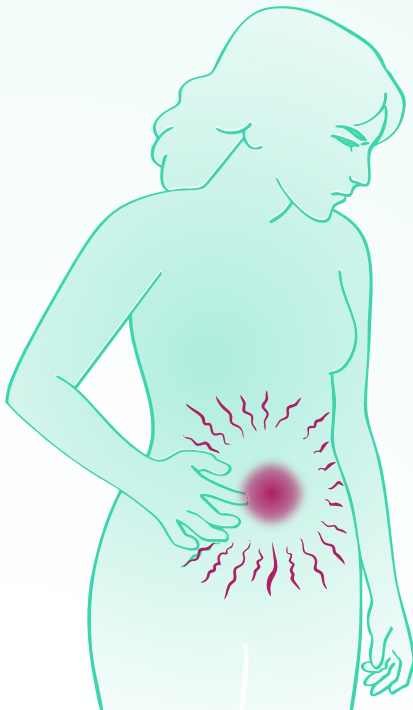
Other symptoms

- Hyponatremia
- Anemia
- Tachycardia



Other neurological symptoms

- Muscle Weakness
- Seizures
- Neuropathic pain



This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack⁴

CONDITIONS^{2,3,5,6}

Metabolic or endocrine disorders:

- Inappropriate antidiuretic hormone secretion (SIADH)
- Pheochromocytoma
- Acute hypoadrenalism (Addisonian crisis)
- Acute hypoparathyroidism
- Hypocalcemic crisis

Hematological conditions:

- Acute hemolytic crisis
- Acute sickle cell crisis
- Familial mediterranean fever

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.⁴

Target Populations for Proactive Screening

High-risk groups and red-flag symptoms



- **Hyponatremia** is a key symptom of AHP and screening should be considered in patients presenting with hyponatremia alongside:¹
 - **Neuropathic symptoms**
 - **Unexplained abdominal pain**
 - **Psychiatric symptoms**
 - **Dark color urine**
- Additional factors that should trigger suspicion of AHP are:^{2,3}
 - **Recent weight loss**
 - **Low carbohydrate diet**
 - Symptoms alongside **certain forms of hormonal contraceptives**
 - History of **recurring symptoms associated with menses**

Defects in the heme biosynthesis pathway results in neurotoxic buildup of ALA and PBG, which is believed to cause disease manifestations across multiple organ systems^{4,5}

Simple biochemical screening tests can help identify AHP early if considered as a differential diagnosis⁶



Click for diagnostic workflow for AHP



Intro



Summary

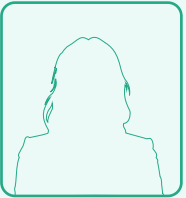
Ref & abbs

AHP Case Scenario: AIP and SIADH in the Diagnostic Journey

Jesuthasan A, Wride M, Esdaile H, et al. An Unexpected Case of Acute Intermittent Porphyria. *Acute Med* 2024;23(1):46-49.

AIP and SIADH in the Diagnostic Journey

Clinical presentation and initial workup¹



Patient: Young* | Female

Presented with:

- A 3-month history of abdominal pain and 2-month history of constipation
- Frequent vomiting with associated weight loss
- Proximal upper limb weakness
- Loss of menses for the past 2 months
- Hypertensive for her age group (> 140/90 mmHg) and had mild tachycardia (> 100 bpm)
- Blood test showed iron deficiency anemia
- Hyponatremia

Notable medical history:

- Had presented to 2 other hospitals in recent weeks with similar symptoms; discharged both times with analgesia and no diagnosis
- Previously investigated for chronic fatigue
- Medications: alverine, codeine, macrogol and lactulose

Diagnostic journey and initial treatment

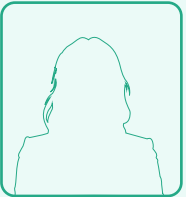
- **Syndrome of inappropriate antidiuretic hormone secretion** managed supportively with IV saline, laxatives, antihypertensive agents (doxazosin) and analgesia (tramadol)
- During hospital admission **AHP was considered as a potential diagnosis that would encompass all symptoms**

This is a real patient case. Individual experiences may vary.

**Exact age of patient not specified in the case report.*

AIP and SIADH in the Diagnostic Journey

Additional clinical investigation¹



Patient: Young* | Female

Tests conducted:

- Serum porphyrin screen
- Urine analysis:

Laboratory test	Laboratory value	Result
Urine PBG	68.5 $\mu\text{mol}/\text{mmol}$ (normal < 1.5 $\mu\text{mol}/\text{mmol}$)	Elevated

Acute intermittent porphyria (AIP) confirmed

The patient was managed symptomatically and referred for neurorehabilitation

Key AIP symptoms in this patient

- Progressive motor weakness
- Abdominal pain
- Hyponatremia
- Hypertension

This is a real patient case. Individual experiences may vary.

**Exact age of patient not specified in the case report*

AHP Considerations for Gynecologists

The information presented is provided for educational purposes and is derived from the cited literature. Healthcare professionals should exercise their independent clinical judgement in determining appropriate screening and diagnostic approaches for individual patients.

Considerations for Gynecologists

Patients with AHP may report worsening of symptoms at specific points of the menstrual cycle¹



- In a patient survey of 100 female patients with AHP, 61% reported the worst symptoms to coincide with the time immediately before menstruation, while 33% reported it during menstruation and 14% after menstruation¹
 - **Perimenopause** was associated with worsening of patient-reported symptoms¹
- Some **contraceptive methods** including progesterone-only pills, depot medroxyprogesterone and combined estrogen-progestin pills are associated with worsening AHP symptoms¹
- Many patients with AHP undergo **unjustified surgical procedures**, including hysterectomies²

A green circular icon containing a white lightbulb with rays emanating from it.

Physiological fluctuations during the menstrual cycle is an important trigger for AHP symptoms¹

Intro



Summary

Ref &
abbs

Gynecological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

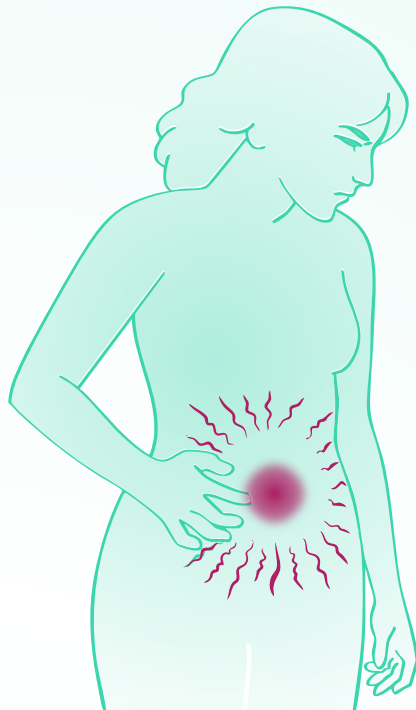
Intro



Summary

Ref &
abbs

SYMPTOMS¹⁻⁵



GI symptoms

- Nausea
- Vomiting
- Abdominal pain



Anemia



Mood or sleep symptoms

- Tiredness
- Trouble sleeping
- Anxiety
- Depression

CONDITIONS^{1,2,6,7}

- Endometriosis
- Menorrhagia
- Ectopic pregnancy
- Physiological fluctuations during the menstrual cycle is an important trigger for AHP symptoms

This is not a comprehensive list of all signs or symptoms of AHP. Most (92%)* patients present with abdominal pain during an acute attack⁴

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.⁴

Target Populations for Proactive Screening

Intro



Summary

Ref &
abbs



High-risk groups and red-flag symptoms

- AHP symptoms may be **triggered by hormonal changes of the menstrual cycle**¹
- All cases of unexplained abdominal pain should be considered for AHP testing, especially if accompanied by additional AHP-associated symptoms such as:^{2,3}
 - Neurovisceral symptoms
 - Psychiatric symptoms
- Some drugs, including hormone therapies are **pro-porphyrinogenic and may trigger AHP symptoms**^{4,5}

Women make up 90% of patients with symptomatic AHP^{1,3}

Attacks are rare before onset of menses or after menopause in these patients³

Consider AHP in any female patient aged 15-50 years with unexplained abdominal pain, neurovisceral and psychiatric symptoms that present cyclically^{2,3}



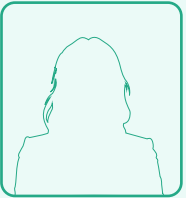
Click for diagnostic workflow
for AHP

AHP Case Scenario: Misdiagnosis of Iron Deficiency Anemia

Burns S, Harmel A, Miller S, et al. Clinical Challenges of Acute Porphyrria in the Young Adult.
Neurohospitalist. 2022;12(2):377-382.

AIP Misdiagnosed as Iron Deficiency Anemia

Clinical presentation and initial workup¹



Patient: 18-year-old | Female

Presented with:

- 5 weeks of abdominal pain, leg cramping and generalized weakness
- Hemoglobin: 4 g/dL

Notable medical history:

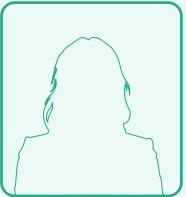
- Iron deficiency anemia
- Menorrhagia

Initial misdiagnosis and treatment

- Iron deficiency and **menorrhagia** treated with iron supplementation and 3 units of packed red blood cells
- 7 days following discharge the patient returned with **new-onset seizure, lower extremity pain, proximal weakness, abdominal pain and hyponatremia**
- Several diagnoses were considered, but all were ruled out and the patient was **discharged without resolution of weakness**
- 10 days later the patient returned with **chest pain, shortness of breath and progressive weakness**

AIP Misdiagnosed as Iron Deficiency Anemia

Additional clinical investigation¹



Patient: 18-year-old | Female

Tests conducted:

- **MRI of brain and spine:** no acute intracranial abnormalities and no identifiable intra- or extradural etiologies causing weakness
- **Lumbar puncture:** Autoimmune, metabolic and infectious screens were negative or within normal limits
- **Nerve conduction and needle electromyography:** decreased amplitude in common peroneal and median nerves with normal conduction velocities, suggestive of sever motor axonal neuropathy
- **Urine analysis of ALA:**

Laboratory test

Laboratory value

Result

Urine ALA

34.6 mg/L (normal 0-5.4 mg/L)

Elevated

Genetic testing: missense mutation, c.583 C>T in the *HMBS* gene

Acute intermittent porphyria (AIP) confirmed

The patient was managed symptomatically and received out-patient physical and occupational therapy follow up

Key AIP symptoms in this patient

- Progressive motor weakness
- Abdominal pain
- Hyponatremia
- Seizure

Intro



Summary

Ref & abbs

Summary



AHP is a rare genetic disease with the potential for multisystem acute and chronic manifestations¹⁻⁷

- Patients may experience potentially life-threatening acute neurovisceral attacks, debilitating chronic symptoms and recurrent symptom flares that impact QoL and may result in long-term complications^{4,8-10}



Due to its rarity and non-specific presentation diagnostic delay is common and patients with AHP are often misdiagnosed¹¹⁻¹⁴



The symptom profile of AHP may mimic many common neurological, psychiatric, GI, renal, gynecological, endocrine, and pediatric conditions. A high clinical suspicion of AHP is therefore warranted to ensure timely diagnosis and initiation of appropriate management¹⁵⁻²⁰

Intro



Summary

Ref &
abbs

Delayed Diagnosis and Misdiagnosis Significantly Contribute to the Burden of AHP

Intro



Patients with AHP may experience

- Potentially life-threatening acute neurological attacks that commonly

Over time, patients with AHP are at risk of developing

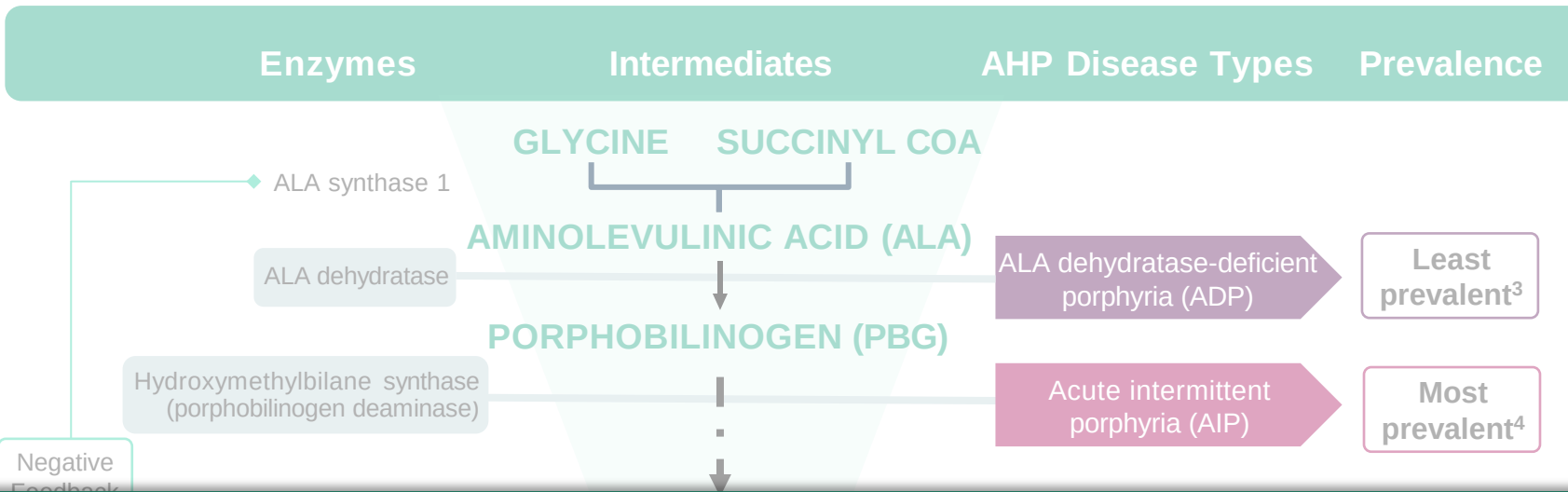
Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet*. 2015;8:201-214;
2. Gouya L, Ventura P, Balwani M, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. 2020;71(5):1546-1558;
3. Simon A, Pompilus F, Querbes W, et al. Patient Perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient*. 2018;11:527-537;
4. Wheeden K, Howe DL, Burrell S, et al. Patient perspective on acute hepatic porphyria with sporadic attacks: A chronic disease with substantial health-related quality of life impacts. *Adv Ther*. 2022;39:4330-4345;
5. Dickey A, Wheeden K, Lyon D, et al. Quantifying the impact of symptomatic acute hepatic porphyria on well-being via patient-reported outcomes: Results from the Porphyria Worldwide Patient Experience Research (POWER) study. *JIMD Rep*. 2022;64:104-113;
6. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
7. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. *Hepatol Commun*. 2019;3(2):193-206;
8. Wikberg A, Andersson C, Lithner F. Signs of neuropathy in the lower legs and feet of patients with acute intermittent porphyria. *J Intern Med*. 2000;248(1):27-32;
9. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. *Br J Haematol*. 2017;176:527-538.

AHP is a Family of Rare Genetic Diseases Caused By Defects in the Heme Biosynthesis Pathway^{1,2}



Induction of ALAS1 leads to systemic accumulation of toxic heme intermediates ALA/PBG^{2,3}

Accumulation of ALA/PBG is believed to cause disease manifestations

Abbreviations:

AHP, acute hepatic porphyria; ALA, aminolevulinic acid; ALAS1, δ -aminolevulinic acid synthase 1; COA, coenzyme-A; PBG, porphobilinogen.

References:

1. Puy H, Deybach JC, Lamoril J, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet.* 1997;60:1373-1383;
2. Balwani M and Desnick RJ. The porphyrias: advances in diagnosis and treatment. *Blood.* 2012;120:4496-4504;
3. Syed YY. Givosiran: A review in acute hepatic porphyria. *Drugs.* 2021;81:841-848;
4. Schmolly K, Rudrapatna V, Beaven S. Recommendations for Recognizing and Diagnosing Acute Hepatic Porphyria in Atypical Patient Populations. *Orphanet J Rare Dis.* 2025;20(1):539.

Heme Synthesis Can Be Induced Through Direct/Indirect ALAS1 Activation, Resulting in Disease Manifestations¹⁻⁶

Intro



Increased heme consumption caused by¹:

- Some drugs metabolized via CYP450*
- Infections and sulfa-containing antibiotics
- Stress



Increased ALAS1 transcription in liver caused by¹:

- Certain drugs and alcohol use



Abbreviations:

AHP, acute hepatic porphyria; ALAS1, δ -aminolevulinic acid synthase 1.

References:

1. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet*. 2015;8:201-214;
2. Balwani M and Desnick RJ. The porphyrias: Advances in diagnosis and treatment. *Blood*. 2012;120:4496-4504;
3. Syed YY. Givosiran: A review in acute hepatic porphyria. *Drugs*. 2021;81:841–848;
4. Simon A, Pompilus F, Querbes W, et al. Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient*. 2018;11:527-537;
5. Elder G, Harper P, Badminton M, et al. The incidence of inherited porphyrias in Europe. *J Inherit Metab Dis*. 2013;36:849-857;
6. Bissell DM, Lai JC, Meister RK, Blanc PD. Role of delta-aminolevulinic acid in the symptoms of acute porphyria. *Am J Med*. 2015;128:313-317;
7. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
8. Marcacci M, Ricci A, Cuoghi C, et al. Challenges in diagnosis and management of acute hepatic porphyrias: From an uncommon pediatric onset to innovative treatments and perspectives. *Orphanet J Rare Dis*. 2022;17(1):160;
9. Badia B, Serrano P, Barile J, et al. Practical recommendations in the treatment of acute and chronic life-threatening infectious diseases in patients with acute hepatic porphyria. *Metabolites*. 2025;15:99.



AHP is Characterized by Chronic and Acute Symptoms¹⁻⁷

Intro

CNS Manifestations^{1,8}

- Confusion
- Anxiety
- Memory loss
- Depression

Long-term Complications⁸

- Primary liver disease
- CKD

Abbreviations:

ANS, autonomic nervous system; CKD, chronic kidney disease; CNS, central nervous system; HCP, hereditary coproporphyria; IBS, irritable bowel syndrome; PNS, peripheral nervous system; VP, variegate porphyria.

References:

1. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. 2020;71(5):1546-1558;
2. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet*. 2015;8:201-214;
3. Simon A, Pompilus F, Querbes W, et al. Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient*. 2018;11:527-537;
4. Bonkovsky HL, Maddukuri VC, Yazici C, et al. Acute porphyrias in the USA: Features of 108 subjects from porphyrias consortium. *Am J Med*. 2014;127:1233-1241;
5. Stewart MF. Review of hepatocellular cancer, hypertension and renal impairment as late complications of acute porphyria and recommendations for patient follow-up. *J Clin Pathol*. 2012;65:976-980;
6. Pallet N, Mami I, Schmitt C, et al. High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. *Kidney Int*. 2015;88:386-395;
7. Andersson C, Bjersing L, Lithner F. The epidemiology of hepatocellular carcinoma in patients with acute intermittent porphyria. *J Intern Med*. 1996;240:195-201;
8. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci*. 2022;363(1):1-10;
9. Ko JJ, Murray S, Merkel M et al. Real-world analysis of symptoms, diagnostic patterns, and provide perspectives on acute hepatic porphyrias. Poster presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018: Philadelphia, PA;
10. Gerischer LM, Scheibe F, Nümann A, et al. Acute porphyrias – A neurological perspective. *Brain Behav*. 2021;11(11):e2389.

AHP Affects HRQoL Regardless of Attack Frequency

Intro

Hypothetical AHP patient archetypes¹⁻⁶

Higher
symptom
severity

Acute attacks

Lower
patient
HRQoL

Patients with AHP experience ongoing disease burden which negatively impacts their QoL^{3,7}

Abbreviations:

AHP, acute hepatic porphyria; HCP, healthcare professional; HRQoL, health-related quality of life; QoL, quality of life.

References:

1. Simon A, Pompilus F, Querbes W, et al. Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient*. 2018;11:527-537;
2. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
3. Wheeden K, Howe DL, Burrell S, et al. Patient perspective on acute hepatic porphyria with sporadic attacks: A chronic disease with substantial health-related quality of life impacts. *Adv Ther*. 2022;39:4330-4345;
4. Dickey A, Wheeden K, Lyon D, et al. Quantifying the impact of symptomatic acute hepatic porphyria on well-being via patient-reported outcomes: Results from the Porphyria Worldwide Patient Experience Research (POWER) study. *JIMD Rep*. 2023;64:104-113;
5. Stein PE, Edel Y, Mansour R et al. Key terms and definitions in acute porphyrias: Results of an international Delphi consensus led by the European porphyria network. *J Inherit Metab Dis*. 2023;46:662-674;
6. Bissell DM, Lai JC, Meister RK, Blanc PD. Role of delta-aminolevulinic acid in the symptoms of acute porphyria. *Am J Med*. 2015;128(3):313-317;
7. Burrell S, Castellano N, Wheeden K, et al. Chronic symptoms reported by patients with acute hepatic porphyria in the POWER study in a subgroup analysis of nonrecurrent patients. Poster presented at IPS 2025, October 9-12, Washington, DC, USA.

Considerations for Neurologists / Pain Specialists

Patients with AHP frequently present to neurologists because symptoms can mimic GBS, PRES, epilepsy, or acute myopathy¹⁻⁴



- Atypical clinical markers such as **abdominal pain**, **hyponatremia**, **autonomic dysfunction**, and **dark urine** are clues indicative of AHP¹⁻³

Early ALA/PBG testing is essential in patients presenting with

11% of patients admitted to neurological wards with acute

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; GBS, Guillain-Barré Syndrome; PBG, porphobilinogen; PRES, Posterior Reversible Encephalopathy Syndrome.

References:

1. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci.* 2022;363(1):1-10;
2. Pischik E, Kazakov V, Kauppinen R. Is screening for urinary porphobilinogen useful among patients with acute polyneuropathy or encephalopathy?. *J Neurol.* 2008;255(7):974-979;
3. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology.* 2020;71(5):1546-1558;
4. Takata T, Kume K, Kokudo Y et al. Acute intermittent porphyria presenting with posterior reversible encephalopathy syndrome, accompanied by prolonged vasoconstriction. *Intern Med.* 2017;56:713-717;
5. Arora H, Baheti G, Jain A, et al. Acute intermittent porphyria with posterior reversible encephalopathy syndrome in pregnancy: A case report. *J Med Res Innov.* 2019;3(1):e000142.



Neurological/Pain Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Abbreviations:

AHP, acute hepatic porphyria; GBS, Guillain-Barré Syndrome; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome

References:

1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
2. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
3. Wheeden K, Howe DL, Burrell S, et al. Patient perspective on acute hepatic porphyria with sporadic attacks: A chronic disease with substantial health-related quality of life impacts. *Adv Ther*. 2022;39:4330-4345;
4. Dickey A, Wheeden K, Lyon D, et al. Quantifying the impact of symptomatic acute hepatic porphyria on well-being via patient-reported outcomes: Results from the Porphyria Worldwide Patient Experience Research (POWER) study. *JIMD Rep*. 2022;64:104-113;
5. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: Updated expert recommendations for primary care physicians. *Am J Med Sci*. 2021;362:113-121;
6. Alhammad RM, Almutawa RA, Ali AS, et al. Clinical features and outcomes of acute intermittent porphyria presenting with acute quadriplegia: A case series and follow-up study. *Eur J Neurol*. 2025;32(6):e70260;
7. Li W, Lian ZY, Mi XJ, Tang J. Acute intermittent porphyria with epilepsy as the initial manifestation and posterior reversible encephalopathy syndrome: A case report. *Case Rep Neurol Med*. 2025;5596570;
8. Sharma SR, Sharma N, Synmon B, Hynniewtaya Y. Porphyria-induced Postpartum Reversible Posterior Encephalopathy Syndrome. *Indian J Crit Care Med*. 2022;26(6):728-730;
9. Wang J, Chen J, Xu K, et al. An easily overlooked disease in the early stages: Acute intermittent porphyria. *BMC Neurol*. 2025;25(1):61;
10. Rao W, Li L, Wu L, et al. A case report of acute intermittent porphyria presenting with reversible cerebral vasoconstriction syndrome. *Medicine (Baltimore)*. 2025;104(8):e41526;
11. Theuriet J, Gerfaud-Valentin M, Durel CA, et al. Neuralgic amyotrophy presentation of acute intermittent porphyria: A case report. *J Peripher Nerv Syst*. 2024;29(4):567-569;
12. Dong W, Zeng B, Wang X, et al. A novel *HMBS* gene mutation in acute intermittent porphyria: A case report of abdominal pain, seizures, and reversible neuroimaging findings. *Front Genet*. 2025;16:1551832;
13. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: "Purple flags"—clinical features that should prompt specific diagnostic testing. *Am J Med Sci*. 2022;363(1):1-10;
14. Barletta EA, Belsuzarri TAB, Urena ARB, Iunes EA. Acute neurological manifestations of porphyrias and its types: A systematic review. *Cardiovasc Hematol Agents Med Chem*. 2021;19(1):3-7;
15. Pacut P, Cannon J, Dixit N, Fan Q. The case of a 37-year-old woman presenting with subacute weakness and paresthesias. *Ann Clin Transl Neurol*. 2025;13(3):639-640;
16. Suh Y, Gandhi J, Seyam O, et al. Neurological and neuropsychiatric manifestations of porphyria. *Int J Neurosci*. 2019;129(12):1226-1233;
17. Musayeva G, Isat E, Yildiz M, et al. Acute hepatic porphyria masquerading as familial mediterranean fever: Results of a cross-sectional porphobilinogen screening. *Orphanet J Rare Dis*. 2026;21(1):168.



Target Populations for Proactive Screening

High-risk groups and red flag symptoms



- **Acute peripheral neuropathy and pain or dysautonomia:**^{1,2}

Any patient with an acute or subacute motor polyneuropathy in combination with moderate-to-severe abdominal or back pain and/or signs of autonomic dysfunction

- **Acute encephalopathy and pain or dysautonomia:**^{1,2}

Any patient with acute or subacute cognitive impairment (encephalopathy) with moderate-to-severe abdominal or back pain and/or autonomic dysfunction

Neurological complications are important components of an AHP attack

Early diagnosis and appropriate management may improve prognosis and may prevent severe neurological complications^{2,3}

Consider AHP as a differential diagnosis in patients

Abbreviations:

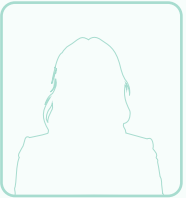
AHP, acute hepatic porphyria; GBS, Guillain-Barré Syndrome; PRES, Posterior Reversible Encephalopathy

References:

1. Gerischer LM, Scheibe F, Nümann A, et al. Acute porphyrias - A neurological perspective. *Brain Behav.* 2021;11(11), e2389;
2. Pischik E, Kazakov, V, Kauppinen, R. Is screening for urinary porphobilinogen useful among patients with acute polyneuropathy or encephalopathy?. *J Neurol.* 2008;255(7):974-979;
3. Barletta EA, Belsuzarri TAB, Urena ARB, Iunes EA. Acute neurological manifestations of porphyrias and its types: A systematic- review. *Cardiovasc Hematol Agents Med Chem.* 2021;19(1):3-7.

AHP Misdiagnosed as Parsonage-Turner Syndrome

Clinical presentation and initial workup¹



Patient: 41-year-old | Female

Presented with:

- Burning pain and electric shock-like sensations in the shoulder and trunk
- Asymmetrical motor weakness in upper limbs affecting arm abduction, shoulder rotation and finger extension
- Dysesthesia
- Nerve conduction study showed decreased nerve action potential amplitude of the superior trunk and brachial plexus
- Needle electromyography showed fibrillations at rest in muscles of the shoulder, forearm and fingers
- Sympathetic skin responses and electrochemical skin conductance were abnormal in both feet

Initial misdiagnosis and treatment

- **Neuralgic amyotrophy** involving the superior trunk of the brachial plexus and the posterior interosseous nerve, possibly associated with small fiber neuropathy
- Symptoms improved initially, but 14 months later she experienced an **acute relapse of symptoms with abdominal burning pain and severe constipation**

Abbreviations:

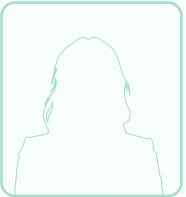
AHP, acute hepatic porphyria.

References:

1. Theuriet J, Gerfaud-Valentin M, Durel CA, et al. Neuralgic amyotrophy presentation of acute intermittent porphyria: A case report. *J Peripher Nerv Syst.* 2024;29(4):567-569.

AHP Misdiagnosed as Parsonage-Turner Syndrome

Additional clinical investigation¹



Patient: 41-year-old | Female

Tests conducted:

- **Nerve conduction study and needle electromyography:** further deterioration of the posterior interosseous nerve function; reappearance of fibrillations in the finger extensor muscles
- **Visual inspection:** Orange colored urine
- **Urine analysis of ALA and PBG:**

Laboratory test	Laboratory value	Result
Urine PBG	34 nmol/mol creatine (normal < 3)	Elevated
Urine ALA	87.4 nmol/mol creatine (normal < 1)	Elevated

Key AIP symptoms in this patient¹

- Progressive motor weakness
- Abdominal burning pain
- Dark urine
- Severe constipation

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ -aminolevulinic acid; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen.

References:

1. Theuriet J, Gerfaud-Valentin M, Durel CA, et al. Neuralgic amyotrophy presentation of acute intermittent porphyria: A case report. *J Peripher Nerv Syst.* 2024;29(4):567-569.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

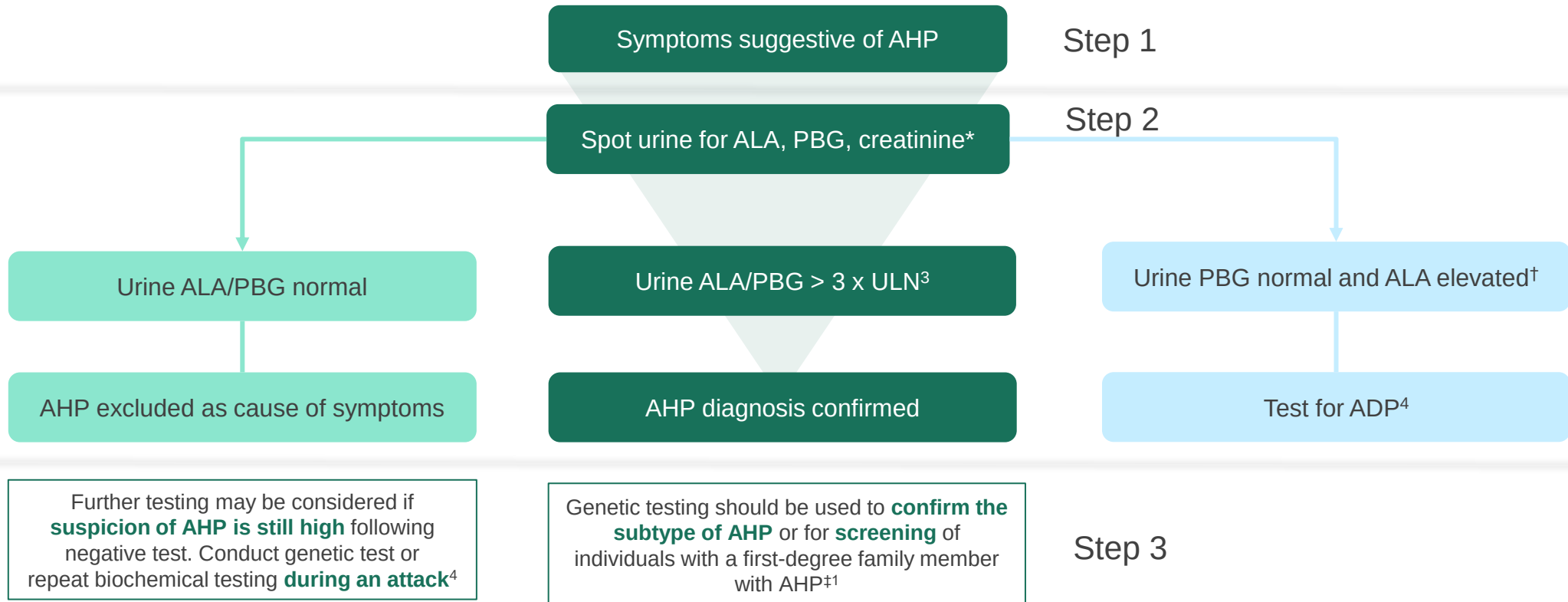


Figure adapted from Wang B et al. *Gastroenterology* 2023;164:484-491 and Moghe A et al. *Hepatology*. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia. [‡]Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med* 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: Updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. *Hepatology*. Published online April 12, 2024.

Considerations for Psychiatrists

Psychiatric syndromes are common in AIP and at times are the presenting or only manifestation¹⁻⁵



- A review encompassing 3867 patients with psychiatric conditions found AIP prevalence to be **20× higher in this cohort compared to the general population**²
- Individuals with AIP have markedly increased risks of **schizophrenia** (RR ≈ 3.6) and **bipolar disorder** (RR ≈ 3.7) compared to individuals without symptomatic AIP; first-degree relatives of individuals with AIP also had elevated risks of schizophrenia (RR ≈ 1.6) and bipolar disorder (RR ≈ 1.8)¹

AHP is rare⁷ but disproportionately present among patients with psychiatric conditions⁴

AHP may masquerade as primary psychiatric disease⁴

Abbreviations:

AHP, acute hepatic porphyria; RR, risk ratio; SSD, schizophrenia spectrum disorder.

References:

1. Cederlöf M, Bergen SE, Larsson H, et al. Acute Intermittent Porphyria: Comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden. *Br J Psychiatry*. 2015;207(6):556-557;
2. Duque-Serrano L, Patarroyo-Rodriguez L, Gotlib D, Molano-Eslava JC. Psychiatric Aspects of Acute Porphyria: a Comprehensive Review. *Curr Psychiatry Rep*. 2018;20(1):5;
3. Bonnot O, Klünemann HH, Sedel F, et al. Diagnostic and Treatment Implications of Psychosis Secondary to Treatable Metabolic Disorders in Adults: A Systematic Review. *Orphanet J Rare Dis*. 2014;9:65;
4. Ellencweig N, Schoenfeld N, Zemishlany Z. Acute intermittent porphyria: Psychosis as the Only Clinical Manifestation. *Isr J Psychiatry Relat Sci*. 2006;43(1):52-56;
5. Vitória-Silva J, Mota J. Porphyria misdiagnosed as schizophrenia nonresponsive to electroconvulsive therapy. *J ECT*. 2019;35(2):e20;
6. Bonnot O, Insua JL, Walterfang M, et al. Development of a suspicion index for secondary schizophrenia using the Delphi method. *Aust N Z J Psychiatry*. 2022;56(5):500-509;
7. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491.

Psychological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
2. Wheeden K, Howe DL, Burrell S, et al. Patient perspective on acute hepatic porphyria with sporadic attacks: A chronic disease with substantial health-related quality of life impacts. *Adv Ther*. 2022;39:4330-4345;
3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: Updated expert recommendations for primary care physicians. *Am J Med Sci*. 2021;362:113–121;
4. Suh Y, Gandhi J, Seyam O, et al. Neurological and neuropsychiatric manifestations of porphyria. *Int J Neurosci*. 2019;129(12):1226-1233;
5. Eroglu S, Birsenogul I. Delirium with delayed diagnosis of hereditary coproporphyria. *Clin Case Rep*. 2022;10(6):e05937;
6. Jain G, Bennett JI, Resch DS, Godwin JE. Schizoaffective disorder with missed diagnosis of acute porphyria: A case report and overview. *Prim Care Companion CNS Disord*. 2011;13(6):PCC.11br01234;
7. Ooi CF, Tang CT, Ting SQ, et al. Managing psychosis in acute intermittent porphyria: A case report on olanzapine use. *Cureus*. 2025;17(6):e85815;
8. Şenel M, Çakmak IB, Gürkan S, et al. Psychiatric presentation of hereditary coproporphyria with coproporphyrinogen oxidase gene mutation c.734 C>T: A case report. *Noro Psikiyatr Ars*. 2025;62(4):390-392;
9. Vitória-Silva J, Mota J. Porphyria misdiagnosed as schizophrenia nonresponsive to electroconvulsive therapy. *J ECT*. 2019;35(2):e20;
10. Kumar B. Acute intermittent porphyria presenting solely with psychosis: A case report and discussion. *Psychosomatics*. 2012;53(5):494-8;
11. Ellencweig N, Schoenfeld N, Zemishlany Z. Acute intermittent porphyria: Psychosis as the only clinical manifestation. *Isr J Psychiatry Relat Sci*. 2006;43(1):52-56;
12. Wolfmeir M, Burits J. Acute Psychosis in variegate porphyria: A case report. *Neuropsychiatr*. 2025;39(3):155-158;
13. Schmolly K, Rudrapatna V, Beaven S. Recommendations for recognizing and diagnosing acute hepatic porphyria in atypical patient populations. *Orphanet J Rare Dis*. 2025;20(1):539;
14. Duque-Serrano L, Patarroyo-Rodriguez L, Gotlib D, Molano-Eslava JC. Psychiatric aspects of acute porphyria: A comprehensive review. *Curr Psychiatry Rep*. 2018;20(1):5;
15. Cederlöf M, Bergen SE, Larsson H, et al. Acute intermittent porphyria: comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden. *Br J Psychiatry*. 2015;207(6):556-557;
16. Bonnot O, Klünemann HH, Sedel F, et al. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: A systematic review. *Orphanet J Rare Dis*. 2014;9:65;
17. Narang N, Banerjee A, Kotwal J, et al. Psychiatric manifestations in three cases of acute intermittent porphyria. *Med J Armed Forces India*. 2003;59(2):171-173.

Target Populations for Proactive Screening

High-risk groups and red flag symptoms



Porphyria testing or liaison with internal medicine is indicated when patients present with:

- Psychosis with abdominal pain^{1,2}
- Atypical or treatment-resistant psychosis, oscillating attention/orientation, fluctuating mood/behavior, or catatonic features

Psychosis may be the sole clinical manifestation of AHP⁶

It is recommended that porphyria is considered as

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Duque-Serrano L, Patarroyo-Rodriguez L, Gotlib D, Molano-Eslava JC. Psychiatric aspects of acute porphyria: A comprehensive review. *Curr Psychiatry Rep.* 2018;20(1):5;
2. Bonnot O, Klünemann HH, Sedel F, et al. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: A systematic review. *Orphanet J Rare Dis.* 2014;9:65;
3. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2019;3(2):193-206;
4. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology.* 2023;164(3):484-491;
5. Cederlöf M, Bergen SE, Larsson H, et al. Acute intermittent porphyria: Comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden. *Br J Psychiatry.* 2015;207(6):556-557;
6. Ellencweig N, Schoenfeld N, Zemishlany Z. Acute intermittent porphyria: Psychosis as the only clinical manifestation. *Isr J Psychiatry Relat Sci.* 2006;43(1):52-56;
7. Narang N, Banerjee A, Kotwal J, et al. Psychiatric manifestations in three cases of acute intermittent porphyria. *Med J Armed Forces India.* 2003;59(2):171-173.

AHP Misdiagnosed as Schizoaffective Disorder

Clinical presentation and initial workup¹



Patient: 66-year-old | Male

Presented with:

- Violent behavior, restlessness, disorientation, delusions and visual hallucinations
- Mental status examination revealed labile affect, limited cognition, and poor insight and judgment
- Rapid and pressured speech
- Skin lesions on the dorsum of the hands and forearms
- Complete blood count, blood glucose, serum creatinine, liver function tests, total bilirubin, albumin, and protein levels were normal; urine toxicology screen was negative

Notable medical history:

- Dementia

Initial misdiagnosis and treatment

- **Schizoaffective disorder** and received treatment of haloperidol, olanzapine, divalproex sodium, lorazepam, fluoxetine, and diphenhydramine
- **Symptoms progressively worsened** with hyperactive delirium, increasingly agitated mental state, atrial fibrillation, rapid heart rate and skin lesions on upper extremities

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Eroglu S, Birsenogul I. Delirium with delayed diagnosis of hereditary coproporphyria. *Clin Case Rep.* 2022;10(6):e05937.

AHP Misdiagnosed as Schizoaffective Disorder

Additional clinical investigation¹



Patient: 66-year-old | Male

Tests conducted:

- Ischemic white matter changes were noted
- **Infectious workup:** negative
- **Urine and stool analysis:**

Laboratory test	Laboratory value	Result
Urine PBG	1.9 mg/L (normal 0.0-2.0 mg/L)	Normal
Urine ALA	Data not available	Normal
Urine Coproporphyrin I (CI)	163 µg/L (normal range 0-15 µg/L)	Elevated

Key HCP symptoms in this patient

- Acute neuropsychiatric symptoms
- Skin lesions
- Dark urine after administering porphyrinogenic medications

Abbreviations:

AHP, acute hepatic porphyria; ALA, δ -aminolevulinic acid; CI, Coproporphyrin I; CIII, Coproporphyrin III; HCP, hereditary coproporphyria; PBG, porphobilinogen.

References:

1. Eroglu S, Birsenogul I. Delirium with delayed diagnosis of hereditary coproporphyria. *Clin Case Rep.* 2022;10(6):e05937.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

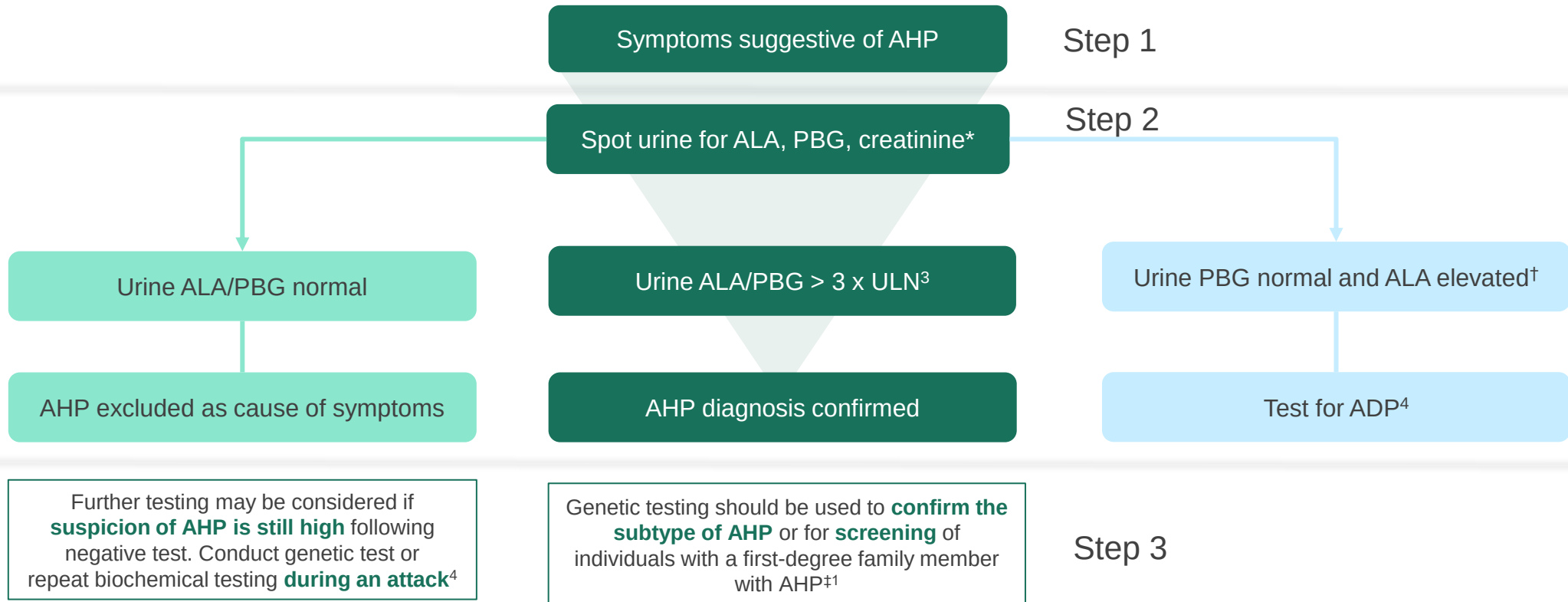


Figure adapted from Wang B et al. *Gastroenterology* 2023;164:484-491 and Moghe A et al. *Hepatology*. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1,2} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med* 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. *Hepatology*. Published online April 12, 2024.

Considerations for Gastroenterologists

Patients with AHP commonly present first and repeatedly in GI settings with severe recurrent abdominal pain but normal imaging and negative standard GI workups¹



- Many patients undergo **years of misdiagnosed GI symptoms**, repeated ER visits, and unnecessary surgeries before AHP is recognized^{1,2}
- Many patients with AIP undergo **unjustified surgical procedures** such as appendectomies and cholecystectomies²

GI symptoms are common manifestations of AHP and overlap with symptoms associated with functional abdominal disorders and IBS¹

A high clinical suspicion is therefore warranted to ensure timely diagnosis and appropriate intervention³

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ER, emergency room; GI, gastrointestinal; IBS, irritable bowel syndrome.

References:

1. Coffin B, Duboc, H. Review article: diagnostic and therapeutic approach to persistent abdominal pain beyond irritable bowel syndrome. *Aliment Pharmacol Ther.* 2022;56(3);419-435;
2. Bonkovsky HL, Maddukuri VC, Yazici C et al . Acute porphyrias in the USA: Features of 108 subjects from porphyria consortium. *Am J Med.* 2014;127(12):1233-1241;
3. American Porphyria. The voice of the patient. Available at: https://porphyriafoundation.org/apf/assets/File/public/patients/APFPFDDMeetingMarch12017-TheVoiceofthePatient_1.pdf (accessed August 10 2026).

GI Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

Intro



SYMPTOMS^{1,2}

GI symptoms

- Severe abdominal pain
- Nausea
- Constipation

CONDITIONS³⁻⁷

- Partial intestinal obstruction
- Irritable bowel syndrome
- Cholecystitis
- Viral hepatitis

Abbreviations:

AHP, acute hepatic porphyria; GI, gastrointestinal.

References:

1. Wang B, Bonkovsky HL, Lim JK, et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
2. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
3. Gerischer LM, Scheibe F, Nümann A, et al. Acute porphyrias—A neurological perspective. *Brain Behav*. 2021;11(11):e2389;
4. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552;
5. Alfadhel M, Saleh N, Alenazi H, et al. Acute intermittent porphyria caused by novel mutation in *HMBS* gene, misdiagnosed as cholecystitis. *Neuropsychiatr Dis Treat*. 2014;10:2135-7;
6. Norman J, Soliman M. Unraveling Complexity: Acute intermittent porphyria complicated by rhabdomyolysis and acute pancreatitis. *Cureus*. 2024;16(7):e65826;
7. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med*. 2025;32;
8. Trier H, Krishnasamy VP, Kasi PM. Clinical manifestations and diagnostic challenges in acute porphyrias. *Case Rep Hematol*. 2013;2013:628602;
9. Bissel DM, Wang B. Acute hepatic porphyria. *J Clin Trans Hepatol*. 2016;3(1):17-26;
10. Armagan S, Williams R, Elias E. A case report of porphyria complicated by PRES: A Trojan horse presenting as dysmenorrhea. *AIM Clinical Cases*. 2025;4:e240882.

patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.²

Target Populations for Proactive Screening



High-risk groups and red-flag symptoms

Patients with severe, persistent and poorly localized abdominal pain, accompanied by:¹

- **Lack of peritoneal irritation**
- **Additional symptoms:** lower limbs and back pain
- **GI symptoms:** nausea, vomiting, constipation

High clinical suspicion of AHP in patients who present with red-flag symptoms may enable timely management, minimise avoidable morbidity, and reduce repeat healthcare utilization¹

Abbreviations:

AHP, acute hepatic porphyria; GI, gastrointestinal.

References:

1. Edel Y, Stein PE, Kawtharany H, et al. Guidelines for the management of acute porphyria: recommendations from the international porphyria network. *Lancet Haematol.* 2026;13:e338-350;
2. Elsaid MI, Li Y, Catalano C, et al. Healthcare Utilization and Cost Burden of Porphyria in Commercially Insured Adults in the United States. *PharmacoEconomics.* 2021;5:89–100.

AHP Misdiagnosed as Partial Intestinal Obstruction

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Presented with:

- Recurrent episodes of severe abdominal pain, nausea, vomiting, constipation
- Numbness of bilateral lower limb extremities

Notable medical history:

- Five hospital admissions due to neurovisceral attacks over the past 2 years

Initial misdiagnosis and treatment

- **Appendicitis;** emergency laparoscopic exploration
- **Partial intestinal obstruction;** conservatively managed
- While awaiting diagnostic laparoscopy, the patient developed **confusion** and was **found to have systemic hypertension**

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552.

AHP Misdiagnosed as Partial Intestinal Obstruction

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Tests conducted:

- Watson and Schwartz test for urine PBG: positive
- Urine analysis:

Laboratory test	Laboratory value	Result
Total porphyrin level	5505.5 nmol/L (normal <300 nmol/L)	Elevated

- Genetic studies: missense mutation, c.517C>T encoding p.R173W in the *HMBS* gene

Key AHP symptoms in this patient

- Confusion
- Hypertension
- Abdominal pain
- Dark urine

Abbreviations:

AHP, acute hepatic porphyria; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen.

References:

1. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

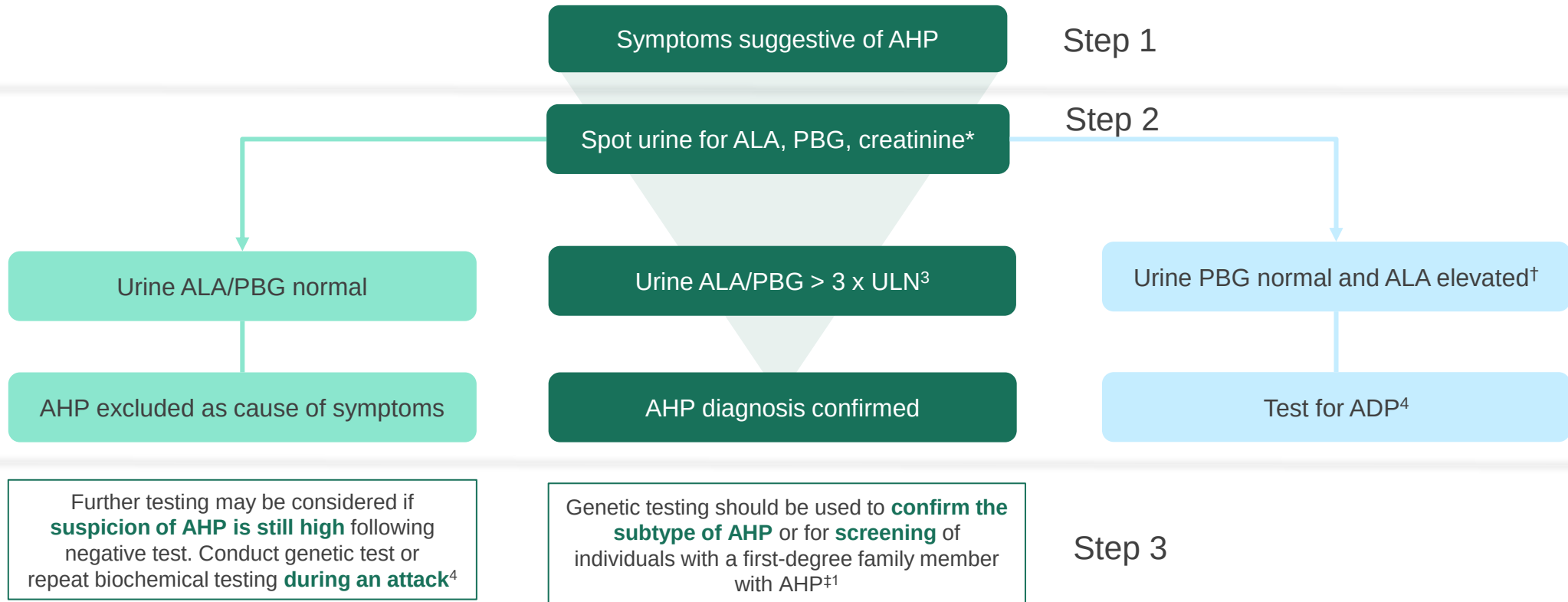


Figure adapted from Wang B et al. *Gastroenterology* 2023;164:484-491 and Moghe A et al. *Hepatology*. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1‡} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med* 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. *Hepatology*. Published online April 12, 2024.

Considerations for the Emergency Department

The emergency department is often the first and sometimes the only setting where patients experiencing severe acute porphyria attacks present.

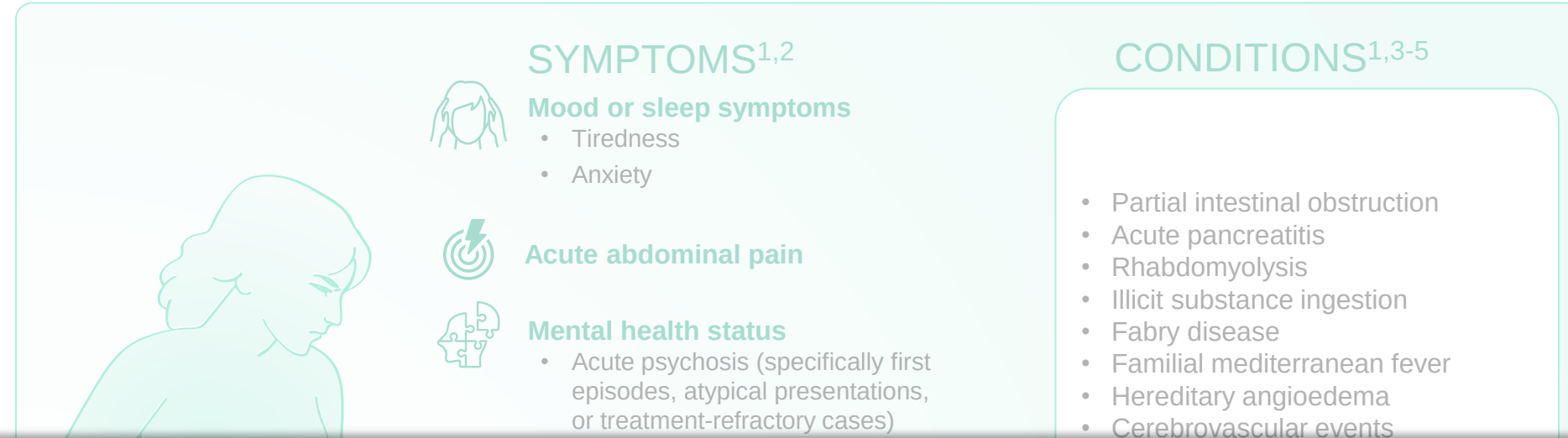
Abbreviations:

AHP, acute hepatic porphyria; ALA, aminolevulinic acid; ED, emergency department; PBG, porphobilinogen.

References:

1. Diehl-Wiesenecker E, Blaschke S, Wohmann N, et al. Detect acute porphyrias in emergency departments (depored) - A pilot study. *Orphanet J Rare Dis.* 2023;18(1):146;
2. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med.* 2025;32;
3. Balwani M and Desnick RJ. The porphyrias: Advances in diagnosis and treatment. *Blood.* 2012;120:4496-4504;
4. Syed YY. Givosiran: A review in acute hepatic porphyria. *Drugs.* 2021;81:841-848;
5. Edel Y, Stein PE, Kawtharany H, et al. Guidelines for the management of acute porphyria: Recommendations from the international porphyria network. *Lancet Haematol.* 2026;13.e338-350;
6. Wang B, Bonkovsky HL, Lim JK et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology.* 2023;164(3):484-491;
7. American Porphyria Foundation. The voice of the patient. Available at: https://porphyriafoundation.org/apf/assets/File/public/patients/APFPFDDMeetingMarch12017-TheVoiceofthePatient_1.pdf. Updated June 01 2026 (accessed September 08 2026);
8. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med.* 2005;142:439-450;
9. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci.* 2021;362(2):113-121.

Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP in the Emergency Department



Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med*. 2025;32;
2. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
3. Pflock S, Mücke HC, Somasundaram R, et al. Common features of rare disease patients in the emergency department: A systematised literature review. *Orphanet J Rare Dis*. 2025;20(1):582;
4. Norman J, Soliman M. Unraveling complexity: Acute intermittent porphyria complicated by rhabdomyolysis and acute pancreatitis. *Cureus*. 2024;16(7):e65826;
5. Marcacci M, Ricci A, Cuoghi C, et al. Challenges in diagnosis and management of acute hepatic porphyrias: From an uncommon pediatric onset to innovative treatments and perspectives. *Orphanet J Rare Dis*. 2022;17(1):160.

Target Populations for Proactive Screening

High-risk groups and red-flag symptoms



Consider AHP in patients presenting with:¹

- Arterial hypertension
- Tachycardia
- Hyponatremia
- Neuropsychiatric symptoms
- Seizures
- T urine
- Previous episodes of abdominal pain

Patients with AIP may spend large amounts of time in the medical system, including multiple visits to the ED and/or hospitalizations²



Click for diagnostic workflow for AHP

Abbreviations:

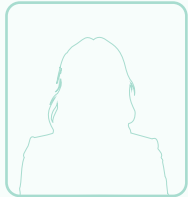
AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ED, emergency department.

References:

1. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med.* 2025;32;
2. American Porphyria Foundation. The voice of the patient. Available at: https://porphyriafoundation.org/apf/assets/File/public/patients/APFPFDDMeetingMarch12017-TheVoiceofthePatient_1.pdf. Updated June 01 2026 (accessed August 10 2026).

AIP Misdiagnosed as Acute Pancreatitis, Acute Kidney Injury, and Possible Rhabdomyolysis

Clinical presentation and initial workup¹



Patient: 34-year-old | Female

Presented at ED with:

- Severe abdominal pain, nausea, and oliguria
- New-onset facial numbness and weakness in her right upper and left lower extremities
- Lack of distinctive 'attack periods'

Notable medical history:

- Anxiety
- Bipolar disorder

Initial misdiagnosis and treatment

- Acute pancreatitis, acute kidney injury, and possible rhabdomyolysis which was managed with IV fluid, pain management and antibiotics
- On Day 3 of hospitalization, grossly dark/wine colored urine was observed

Abbreviations:

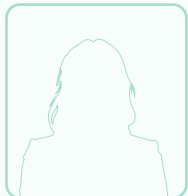
AIP, acute intermittent porphyria; ED, emergency department; GBS, Guillain-Barré syndrome; IV, intravenous.

References:

1. Norman J, Soliman M. Unraveling complexity: Acute intermittent porphyria complicated by rhabdomyolysis and acute pancreatitis. *Cureus*. 2024;16(7):e65826.

AIP Misdiagnosed as Acute Pancreatitis, Acute Kidney Injury, and Possible Rhabdomyolysis

Additional clinical investigation¹



Patient: 34-year-old | Female

Tests conducted:

- Urine analysis (24 hours):

Laboratory test	Laboratory value	Result
Uroporphyrin I	499.3 mcg (normal 4.1-22.4 mcg/24 h)	Elevated
Uroporphyrin III	190.4 mcg (normal 0.7-7.4 mcg/24 h)	Elevated
Heptacarboxylporphyrin	55.4 mcg (normal ≤ 3.3 mcg/24 h)	Elevated
Hexacarboxylporphyrin	2.4 mcg (normal ≤ 10mcg/24 h)	Normal
Pentacarboxylporphyrin	24.4 mcg (normal ≤ 4.6 mcg/24 h)	Elevated
Coproporphyrin I	62 mcg (normal 7.1-48.7 mcg/24 h)	Elevated
Total porphyrin count	1049.3 mcg (normal 35.0-210.7 mcg/24 h)	Elevated

Key AIP symptoms in this patient

- Abdominal pain
- Neurological symptoms
- Dark urine

Abbreviations:

AIP, acute intermittent porphyria; h, hours.

References:

1. Norman J, Soliman M. Unraveling complexity: Acute intermittent porphyria complicated by rhabdomyolysis and acute pancreatitis. *Cureus*. 2024;16(7):e65826.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

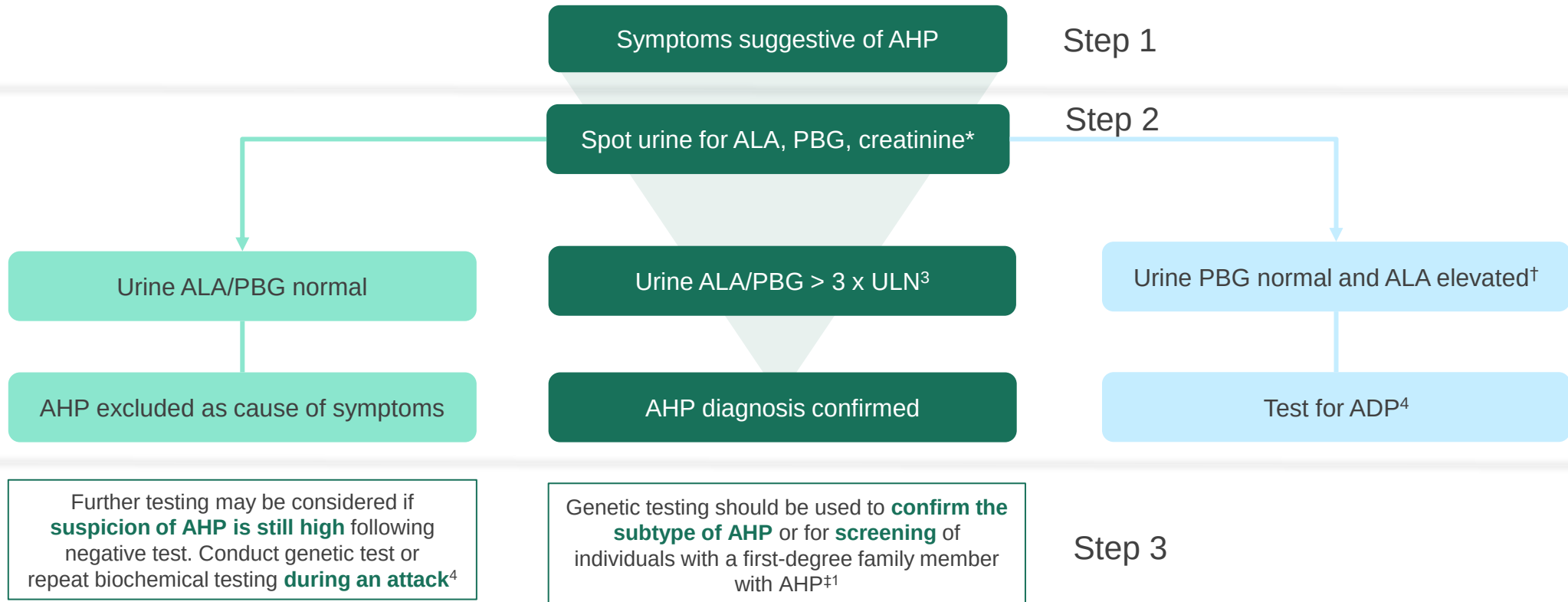


Figure adapted from Wang B et al. *Gastroenterology* 2023;164:484-491 and Moghe A et al. *Hepatology*. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1‡} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med* 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. *Hepatology*. Published online April 12, 2024.

Considerations for Nephrologists



Patients with AHP are at increased risk of CKD and hypertension^{1,2}

- Porphyria-associated kidney disease is associated with an annual decline in eGFR of approximately 1 ml/min per 1.73m²; among patients with PAKD, approximately 60% had concomitant hypertension¹
 - PAKD is postulated to occur due to ALA and PBG-mediated cytotoxic effects on proximal tubular cells¹
- During acute attacks systemic arterial hypertension is often observed, which can result in chronic hypertension in some patients and may be a contributing factor to progressive renal impairment^{1,2}



Chronic kidney disease is a common long-term complication of AHP^{1,3}

Ensuring control of systemic hypertension is recommended to decrease risk of CKD in patients with AHP¹

Abbreviations:

ALA, δ -aminolevulinic acid; AHP, acute hepatic porphyria; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PAKD, porphyria-associated kidney disease; PBG, porphobilinogen.

References:

1. Wang B, Bonkovsky HL, Lim JK et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
2. Pallet N, Karras A, Thervet E, et al. Porphyria and kidney diseases. *CKJ Review*. 2018;11(2):191-197;
3. Ricci A, Carmine Guida C, Manzini P, et al. Kidney involvement in acute hepatic porphyrias: Pathophysiology and diagnostic implications. *Diagnostics*. 2021;11(12):2324.



Nephrological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP



Abbreviations:

AHP, acute hepatic porphyria; CKD, chronic kidney disease; EPO, erythropoietin.

References:

1. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552;
2. Ricci A, Carmine Guida C, Manzini P, et al. Kidney involvement in acute hepatic porphyrias: Pathophysiology and diagnostic implications. *Diagnostics*. 2021;11(12):2324;
3. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558.

All symptoms can be both acute and chronic unless otherwise stated. *Results from EXPLORE A, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (N=112). Eligible patients had experienced three or more attacks in the prior 12 months or were receiving prophylactic treatment.²

Target Populations for Proactive Screening

High-risk groups and red-flag symptoms



AHP should be considered in patients with lower than normal creatinine clearance in the absence of a clear etiology for renal impairment, especially those who still have attacks and those who are hypertensive¹

- Porphyric patients have been reported to have signs of:²
 - Proximal tubulointerstitial insufficiency (proteinuria, impaired EPO production)
 - Oxidative damage (increased urinary excretion of lipoperoxides)

The diagnostic workup of AHPs should include a baseline evaluation of renal function and annual monitoring of the progression of kidney disease^{2,3}

Abbreviations:

AHP, acute hepatic porphyria; CKD, chronic kidney disease; EPO, erythropoietin.

References:

1. Andersson C, Wikberg A, Stegmayer B et al. Renal symptomatology in patients with acute intermittent porphyria. A population-based study. *JIM*. 2001;248(4):219-325;
2. Wang B, Naik H, McDonough C. Logitudinal study of acute hepatic porphyrias in the US: baseline features of 400 subjects from the Porphyrrias Consortium. Poster presented at: AASLD: The Liver Meeting; November 7-11, 2025; Washington, D.C;
3. Ricci A, Carmine Guida C, Manzini P, et al. Kidney involvement in acute hepatic porphyrias: Pathophysiology and diagnostic implications. *Diagnostics*. 2021;11(12):2324;
4. Wang B, Bonkovsky HL, Lim JK et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491.

AIP Misdiagnosed as Renal Calculi and Drug-Induced Acute Interstitial Nephritis

Clinical presentation and initial workup¹



Patient: 33-year-old | Male

Presented with:

- Neurovisceral attack with fever, followed by neurovisceral attack complicated with transient hyponatremia and transiently high serum creatinine levels

Notable medical history:

- Five acute hospital admissions over two years due to neurovisceral attacks
- Medication: nonsteroidal anti-inflammatory drug twice a day for 6 weeks

Initial misdiagnosis and treatment

- Renal colic, followed by **interstitial nephritis** based on prolonged use of nonsteroidal anti-inflammatory drug
- The patient experienced **several attacks**, the last presenting with recurrent episodes of severe abdominal pain, nausea, vomiting, constipation, and numbness of bilateral lower limb extremities

Abbreviations:

AIP, acute intermittent porphyria.

References:

1. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552.

AIP Misdiagnosed as Renal Calculi and Drug-Induced Acute Interstitial Nephritis

Additional clinical investigation¹



Patient: 33-year-old | Male

Tests conducted:

- Watson and Schwartz test for urine PBG: positive
- Urine analysis:

Laboratory test	Laboratory value	Result
Total porphyrin level	5505.5 nmol/L (normal <300 nmol/L)	Elevated

- Genetic studies: missense mutation, c.517C>T encoding p.R173W in the *HMBS* gene

Key AHP symptoms in this patient

- Confusion
- Hypertension
- Abdominal pain
- Dark urine

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen.

References:

1. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes*. 2018;11(1):552.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

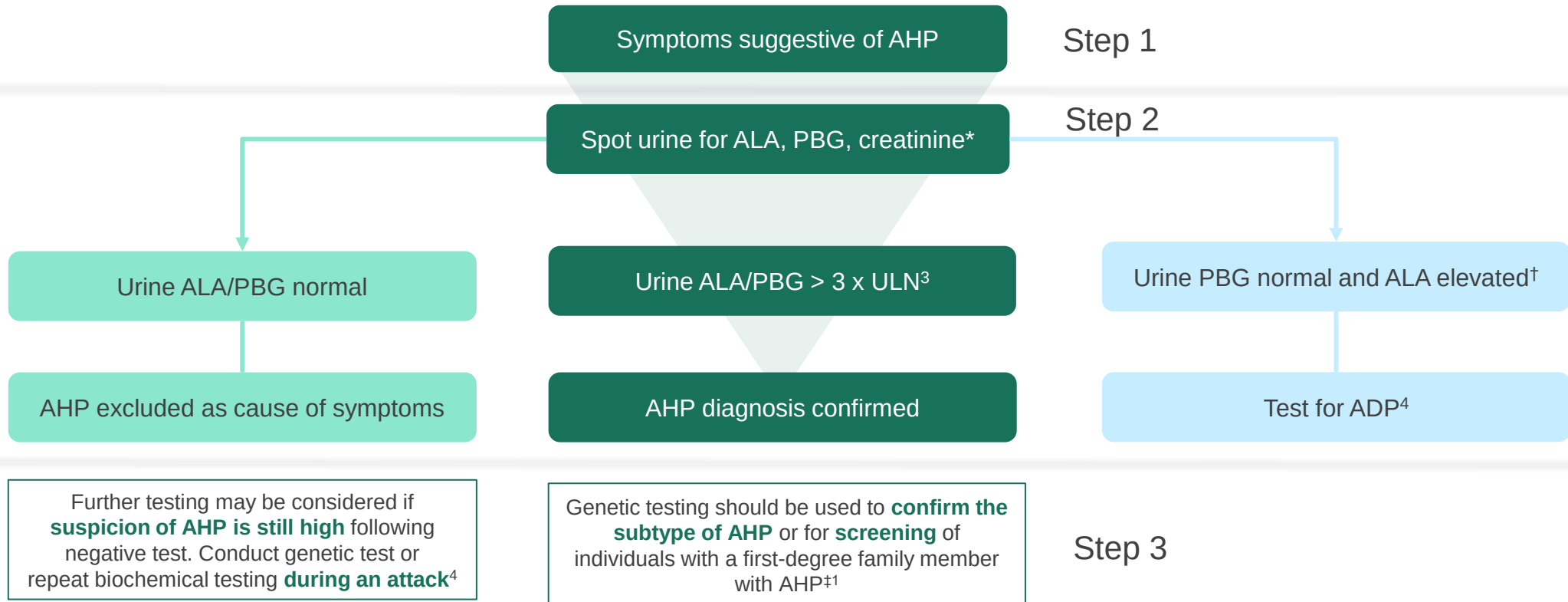


Figure adapted from Wang B et al. Gastroenterology 2023;164:484-491 and Moghe A et al. Hepatology. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1,2} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. Gastroenterology. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. Ann Intern Med 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. Am J Med Sci 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. Hepatology. Published online April 12, 2024.

Considerations for Pediatricians

AHP most commonly present in women aged 15-50 years, but it can present in men and women at any age¹⁻⁴



- Although rare, published cases of AHP manifesting in **infants, children and adolescence** highlight the importance of considering this diagnosis in the pediatric setting²⁻⁴
- **Hormonal changes during adolescence** including dramatic changes in liver metabolism, or initiation of the menstrual cycle can trigger attacks²
- **Family screening and genetic counseling** is warranted to inform of risks of acute attacks among family members¹



AHP typically presents in adults and may therefore be under-recognized in pediatric populations³

High clinical suspicion is required for early recognition and appropriate intervention³

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Wang B, Bonkovsky HL, Lim JK et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
2. Dukkupati SS, Terschluse J, Thodeson D, et al. Porphyrinic encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep*. 2025;13:2050313X241298532;
3. Chakraborty A, Muranjan M, Karande S, et al. Porphyrrias: Uncommon disorders masquerading as common childhood diseases. *J Postgrad Med*. 2023;69(3):164-171;
4. Roach AN, Barkley H, Rodriquez C, et al. Profound hypotonia in an infant with δ -aminolevulinic acid dehydratase deficient porphyria. *Eur J Hum Genet*. 2025;33(8):1080-1083.



Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP in Pediatric Populations

SYMPTOMS¹⁻⁸

Mood or sleep symptoms

CONDITIONS¹⁻⁶

- Partial intestinal obstruction

Abbreviations:

AHP, acute hepatic porphyria.

References:

1. Rao W, Li L, Wu L, et al. A case report of acute intermittent porphyria presenting with reversible cerebral vasoconstriction syndrome. *Medicine (Baltimore)*. 2025;104(8):e41526;
2. Dukkupati SS, Terschluse J, Thodeson D, et al. Porphyric encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep*. 2025;13:2050313X241298532;
3. Gertz B, Mullen M, Pesavento T. An adolescent female with disordered eating and cannabis use found to have acute intermittent porphyria. *Case Rep Psychiatry*. 2025;2025:8875138;
4. Chakraborty A, Muranjan M, Karande S, et al. Porphyrias: Uncommon disorders masquerading as common childhood diseases. *J Postgrad Med*. 2023;69(3):164-171;
5. Roach AN, Barkley H, Rodriguez C, et al. Profound hypotonia in an infant with δ -aminolevulinic acid dehydratase deficient porphyria. *Eur J Hum Genet*. 2025;33(8):1080-1083;
6. Marcacci M, Ricci A, Cuogi C et al. Challenges in diagnosis and management of acute hepatic porphyrias: From an uncommon pediatric onset to innovative treatments and perspectives. *Orphanet J Rare Dis*. 2022;17(1):160;
7. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
8. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med*. 2025;32:30-38.

Target Populations for Proactive Screening

High-risk groups and red-flag symptoms



Unexplained neurovisceral or phototoxic symptoms should cause suspicion of AHP in pediatric patients and trigger proactive biochemical testing^{1,2}

- Pink/red coloured urine or staining of the diaper may be indicative of AHP
- AHP should also be considered in patients with psychiatric and neurological manifestations, especially in the context of first presentation, atypical presentation or treatment-refractory cases

Medical history may reveal family members with previous symptomatic disease; however, this may be in the absence of an associated AHP diagnosis¹

Due to the overall **low penetrance of pathogenic disease**, a history of symptomatic family members may not be present¹

Abbreviations:

AHP, acute hepatic porphyria

References:

1. Chakraborty A, Muranjan M, Karande S, et al. Porphyrrias: Uncommon disorders masquerading as common childhood diseases. *J Postgrad Med.* 2023;69(3):164-171;
2. Moreira S, Ferreira F, Guimas A, et al. Acute porphyria screening protocol in the emergency department: A strategy for early diagnosis. *Port J Intern Med.* 2025;32:30-38.



AHP Misdiagnosed as New-Onset Seizures/Encephalopathy

Clinical presentation and initial workup¹



Patient: 15-year-old | Female

Presented with:

- New-onset tonic-clonic seizures, confusion, unresponsiveness with stiffening of her extremities
- Diffuse sharp abdominal pain, hypertension, hyponatremia, emaciation, anxiousness, vomiting and minimal oral intake
- Brain MRI showing bilateral relatively symmetric areas of cortical signal within the frontal, parietal, and occipital lobes

Notable medical history:

Clinical presentation and initial management

- **Encephalitis** treated with corticosteroids, IV immunoglobulin, and anti-hypertensive drugs
- **Cannabis hyperemesis syndrome** treated with analgesic medication and serotonin antagonist on parenteral nutrition until abdominal pain and emesis improved
- **SIADH** treated with fluid restriction

Abbreviations:

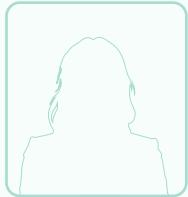
AHP, acute hepatic porphyria; MRI, magnetic resonance imaging; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

References:

1. Dukkupati SS, Terschluse J, Thodeson D, et al. Porphyric encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep.* 2025;13:2050313X241298532.

AHP Misdiagnosed as New-Onset Seizures/Encephalopathy

Additional clinical investigation¹



Patient: 15-year-old | Female

Tests conducted:

• Urine analysis:

Laboratory test	Laboratory value	Result
Random PBG	314.5 µmol/L (normal <9 µmol/L)	Elevated
Uroporphyrin	87 µmol/molCRT (normal 0–4 µmol/molCRT)	Elevated
Heptacarboxylate	6 µmol/molCRT (normal 0–2 µmol/molCRT)	Elevated
Coproporphyrin I	10 µmol/molCRT (normal <30 nmol/molCRT)	Elevated
Coproporphyrin II	82 µmol/molCRT (normal <20 µmol/molCRT)	Elevated

Key AIP symptoms in this patient

- Hypertension
- Abdominal pain
- Dark urine

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ -aminolevulinic acid; CRT, creatinine; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen.

References:

1. Dukkupati SS, Terschluse J, Thodeson D, et al. Porphyrinic encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep.* 2025;13:2050313X241298532.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

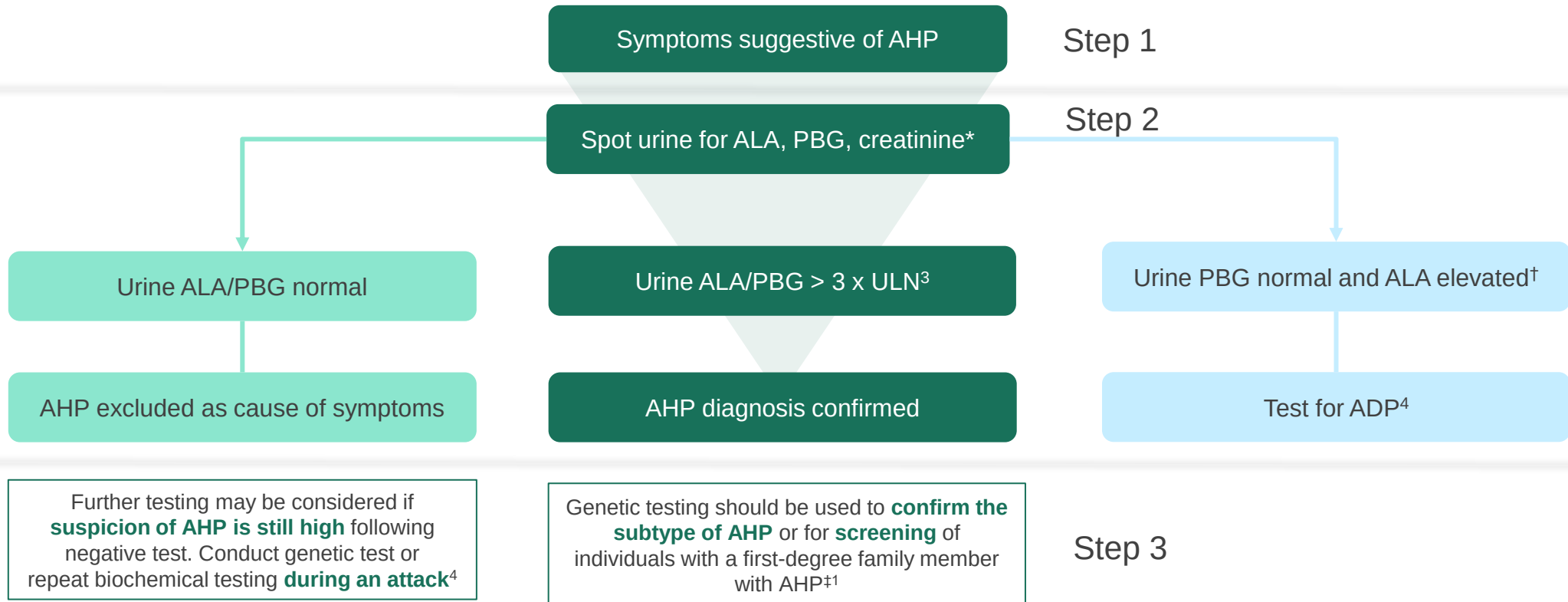


Figure adapted from Wang B et al. Gastroenterology 2023;164:484-491 and Moghe A et al. Hepatology. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1,2} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. Gastroenterology. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. Ann Intern Med 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. Am J Med Sci 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. Hepatology. Published online April 12, 2024.

Considerations for Endocrinologist/Metabolic Specialists and Hematologists

AHP is a rare genetic disease caused by deficiency in the heme biosynthesis pathway^{1,2}

- Known triggers for AHP attacks include:
 - Hormonal changes during adolescence³
 - Physiological fluctuations during the menstrual cycle⁴
 - Rapid weight loss⁵

Consider AHP in patients with unexplained hyponatremia, cyclical or hormonally linked symptoms, metabolic disturbances, or hematologic

Abbreviations:

AHP, acute hepatic porphyria

References:

1. Puy H, Deybach JC, Lamoril J, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet.* 1997;60:1373-1383;
2. Balwani M and Desnick RJ. The porphyrias: Advances in diagnosis and treatment. *Blood.* 2012;120:4496-4504;
3. Dukkipati SS, Terschluse J, Thodeson D, et al. Porphyric encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep.* 2025;13:2050313X241298532;
4. Leaf R, Rebeiz L, Pocius K, et al. Reproductive health across the lifespan in acute hepatic porphyria. *Blood (American Society of Hematology).* 2025; 146:1098-1099;
5. Wang B, Rudnick S, Cengia B et al. Acute hepatic porphyrias: Review and recent progress. *Hepatol Commun.* 2019;3(2):193-206;
6. Norman J, Soliman M. unraveling complexity: Acute intermittent porphyria complicated by rhabdomyolysis and acute pancreatitis. *Cureus.* 2024;16(7):e65826.

Endocrine/Metabolic/Hematological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP



Abbreviations:

AHP, acute hepatic porphyria; GI, gastrointestinal; SIADH, inappropriate antidiuretic hormone secretion.

References:

1. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci*. 2022;363(1):1-10;
2. Burns S, Harmel A, Miller S, et al. Clinical challenges of acute porphyria in the young adult. *Neurohospitalist*. 2022;12(2):377-382;
3. Ventura P, Cappellini MD, Biolcati G et al. A challenging diagnosis for potential fatal diseases: Recommendations for diagnosing acute porphyrias. *Eur J Intern Med*. 2014;25(6):497-505;
4. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
5. Jesuthasan A, Wride M, Esdaile H et al. An unexpected case of acute intermittent porphyria. *Acute Med*. 2024;23(1):46-49;
6. Musayeva G, Isat E, Yiliz M, et al. Acute hepatic porphyria masquerading as familial mediterranean fever: results of a cross-sectional porphobilinogen screening. *Orphanet J Rare Dis*. 2026;21(1):168.

Target Populations for Proactive Screening

High-risk groups and red-flag symptoms



- **Hyponatremia** is a key symptom of AHP and screening should be considered in patients presenting with hyponatremia alongside:¹
 - Neuropathic symptoms
 - Unexplained abdominal pain
 - Psychiatric symptoms
 - Dark colour urine

Defects in the heme biosynthesis pathway results in neurotoxic buildup of ALA and PBG, which is believed to cause disease manifestations across multiple organ systems^{4,5}

Simple biochemical screening tests can

Abbreviations:

AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen.

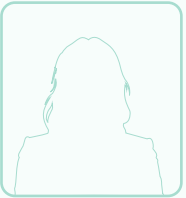
References:

1. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci*. 2022;363(1):1-10;
2. Leaf R, Rebeiz L, Pocius K, et al. Reproductive health across the lifespan in acute hepatic porphyria. *Blood (American Society of Hematology)*. 2025; 146:1098-1099;
3. Wang B, Rudnick S, Cengia B et al. Acute hepatic porphyrias: Review and recent progress. *Hepatol Commun*. 2019;3(2):193-206;
4. Balwani M and Desnick RJ. The porphyrias: Advances in diagnosis and treatment. *Blood*. 2012;120:4496-4504;
5. Syed YY. Givosiran: A review in acute hepatic porphyria. *Drugs*. 2021;81:841-848;
6. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491.



AIP Misdiagnosed as SIADH

Clinical presentation and initial workup¹



Patient: Young* | Female

Presented with:

- A 3-month history of abdominal pain and 2-month history of constipation
- Frequent vomiting with associated weight loss
- Proximal upper limb weakness
- Loss of menses for the past 2 months
- Hypertensive for her age group ($> 140/90$ mmHg) and had mild tachycardia (> 100 bpm)
- Blood test showed iron deficiency anemia
- Hyponatremia

Initial misdiagnosis and treatment

- Syndrome of inappropriate antidiuretic hormone secretion managed supportively with IV saline, laxatives, antihypertensive agents (doxazosin) and analgesia (tramadol)
- During hospital admission **AHP was considered as a potential diagnosis that would encompass all symptoms**

Abbreviations:

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; bpm, beats per minute; IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

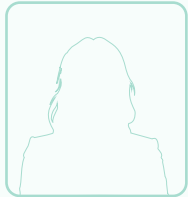
References:

1. Jesuthasan A, Wride M, Esdaile H et al. An unexpected case of acute intermittent porphyria. *Acute Med.* 2024;23(1):46-49.

*Exact age of patient not specified in the case report.

AIP Misdiagnosed as SIADH

Additional clinical investigation¹



Patient: Young* | Female

Tests conducted:

- Serum porphyrin screen
- Urine analysis:

Laboratory test	Laboratory value	Result
Urine PBG	68.5 µmol/mmol (normal < 1.5 µmol/mmol)	Elevated

Key AIP symptoms in this patient

- Progressive motor weakness
- Abdominal pain
- Hyponatremia
- Hypertension

Acute intermittent porphyria (AIP) confirmed

Abbreviations:

AIP, acute intermittent porphyria; PBG, porphobilinogen; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

References:

1. Jesuthasan A, Wride M, Esdaile H et al. An unexpected case of acute intermittent porphyria. *Acute Med.* 2024;23(1):46-49.

¹Exact age of patient not specified in the case report

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

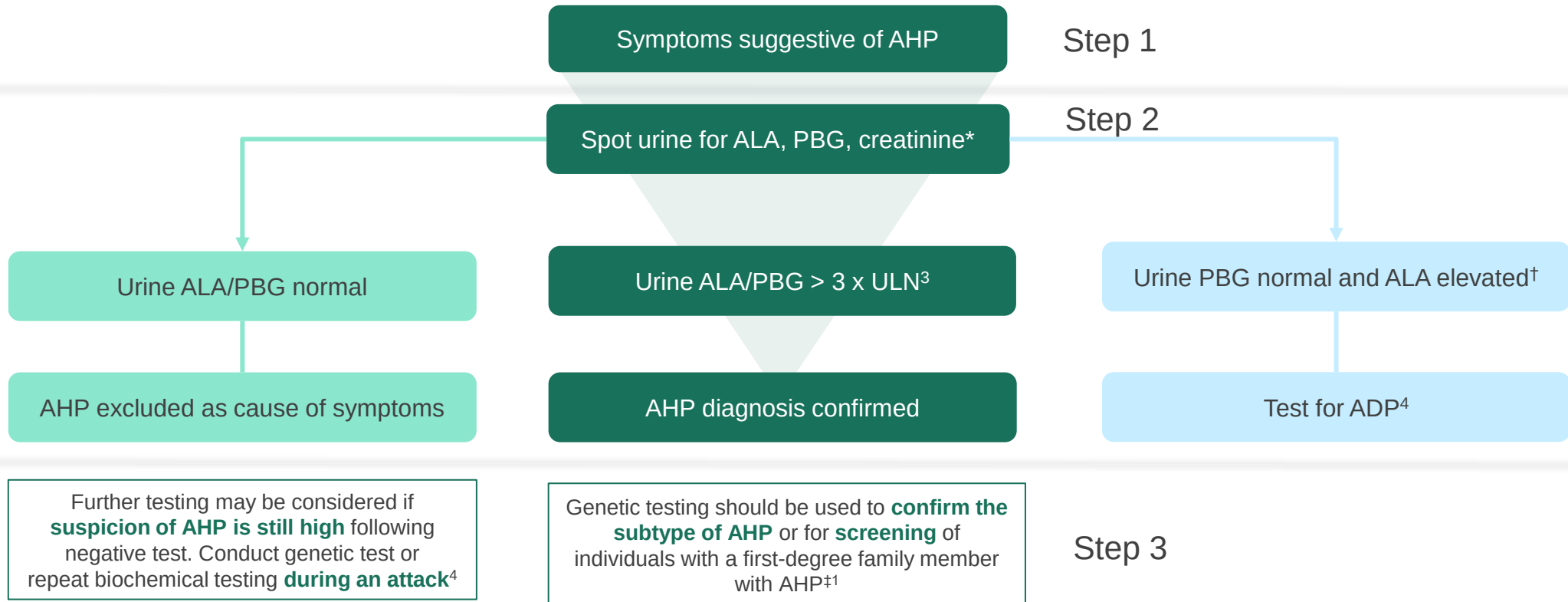


Figure adapted from Wang B et al. Gastroenterology 2023;164:484-491 and Moghe A et al. Hepatology. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1,2} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. Gastroenterology. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. Ann Intern Med 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. Am J Med Sci 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. Hepatology. Published online April 12, 2024.

Considerations for Gynecologists

Patients with AHP may report worsening of symptoms at specific points of the menstrual cycle¹



- In a patient survey of 100 female patients with AHP, 61% reported the worst symptoms to coincide with the time immediately before menstruation, while 33% reported it during menstruation and 14% after menstruation¹
 - **Perimenopause** was associated with worsening of patient-reported symptoms¹
- Some **contraceptive methods** including progesterone-only pills, depot medroxyprogesterone and combined estrogen-progestin pills are associated with worsening AHP symptoms¹
- Many patients with AHP undergo **unjustified surgical procedures**, including hysterectomies²



Physiological fluctuations during the menstrual cycle is an important trigger for AHP symptoms¹

Abbreviations

AHP, acute hepatic porphyria.

References:

1. Leaf R, Rebeiz L, Pocius K, et al. Reproductive health across the lifespan in acute hepatic porphyria. *Blood (American Society of Hematology)*. 2025; 146:1098-1099;
2. Bonkovsky HL, Maddukuri V, Yazici C, et al. Acute porphyrias in the USA: Features of 108 subjects from porphyrias consortium. *Am J Med*. 2014; 127(12):1233-1241.



Gynecological Symptoms and Associated Differential Diagnoses That Should Trigger Suspicion of AHP

SYMPTOMS¹⁻⁵

CONDITIONS^{1,2,6,7}

GI symptoms

- Nausea
- Vomiting
- Abdominal pain

Anemia

- Endometriosis
- Menorrhagia
- Ectopic pregnancy
- Physiological fluctuations during the menstrual cycle is an important trigger for AHP symptoms

Abbreviations:

AHP, acute hepatic porphyria; GI, gastrointestinal.

References:

1. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci*. 2022;363(1):1-10;
2. Burns S, Harmel A, Miller S, et al. Clinical challenges of acute porphyria in the young adult. *Neurohospitalist*. 2022;12(2):377-382;
3. Ventura P, Cappellini MD, Biolcati G et al. A challenging diagnosis for potential fatal diseases: Recommendations for diagnosing acute porphyrias. *Eur J Intern Med*. 2014;25(6):497-505;
4. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2020;71(5):1546-1558;
5. Jesuthasan A, Wride M, Esdaile H et al. An unexpected case of acute intermittent porphyria. *Acute Med*. 2024;23(1):46-49;
6. Leaf R, Rebeiz L, Pocius K, et al. Reproductive health across the lifespan in acute hepatic porphyria. *Blood (American Society of Hematology)*. 2025;146:1098-1099;
7. Ko JJ, Murray S, Merkel M et al. Real-world analysis of symptoms, diagnostic patterns, and provide perspectives on acute hepatic porphyrias. Poster presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018: Philadelphia, PA.

Target Populations for Proactive Screening



High-risk groups and red-flag symptoms

- AHP symptoms may be **triggered by hormonal changes of the menstrual cycle**¹
- All cases of unexplained abdominal pain should be considered for AHP testing, especially if accompanied by additional AHP-associated symptoms such as:^{2,3}
 - Neurovisceral symptoms
 - Psychiatric symptoms

Women make up 90% of patients with symptomatic AHP^{1,3}

Attacks are rare before onset of menses or after menopause in these patients³

Abbreviations

AHP, acute hepatic porphyria.

References:

1. Leaf R, Rebeiz L, Pocius K, et al. Reproductive health across the lifespan in acute hepatic porphyria. *Blood (American Society of Hematology)*. 2025; 146:1098-1099;
2. Duque-Serrano L, Patarroyo-Rodriguez L et al. Psychiatric aspects of acute porphyria: A comprehensive review. *Curr Psychiatry Rep*. 2018;20(1):5;
3. Wang B, Bonkovsky HL, Lim JK, et al. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491;
4. Ma CD, Bonkovsky HL. Elagolix is porphyrogenic and may induce porphyric attacks in patients with the acute hepatic porphyrias. *Mol Genet Metab Rep*. 2022;33:100915;
5. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. *Hepatol Commun*. 2019;3(2):193-206.

AIP Misdiagnosed as Iron Deficiency Anemia

Clinical presentation and initial workup¹



Patient: 18-year-old | Female

Presented with:

- 5 weeks of abdominal pain, leg cramping and generalized weakness
- Hemoglobin: 4 g/dL

Notable medical history:

- Iron deficiency anemia
- Menorrhagia

Initial misdiagnosis and treatment

- Iron deficiency and **menorrhagia** treated with iron supplementation and 3 units of packed red blood cells
- 7 days following discharge the patient returned with **new-onset seizure, lower extremity pain, proximal weakness, abdominal pain and hyponatremia**
- Several diagnoses were considered, but all were ruled out and the patient was **discharged without resolution of weakness**

Abbreviations:

AIP, acute intermittent porphyria.

References:

1. Burns S, Harmel A, Miller S, et al. Clinical challenges of acute porphyria in the young adult. *Neurohospitalist*. 2022;12(2):377-382.

AIP Misdiagnosed as Iron Deficiency Anemia

Additional clinical investigation¹



Patient: 18-year-old | Female

Tests conducted:

- **MRI of brain and spine:** no acute intracranial abnormalities and no identifiable intra- or extradural etiologies causing weakness
- **Lumbar puncture:** Autoimmune, metabolic and infectious screens were negative or within normal limits
- **Nerve conduction and needle electromyography:** decreased amplitude in common peroneal and median nerves with normal conduction velocities, suggestive of sever motor axonal neuropathy
- **Urine analysis of ALA:**

Laboratory test	Laboratory value	Result
Urine ALA	34.6 mg/L (normal 0-5.4 mg/L)	Elevated

Genetic testing: missense mutation, c.583 C>T in the *HMBS* gene

Key AIP symptoms in this patient

- Progressive motor weakness
- Abdominal pain
- Hyponatremia
- Seizure

Abbreviations:

AIP, acute intermittent porphyria; ALA, δ -aminolevulinic acid; HMBS, hydroxymethylbilane synthase; MRI, magnetic resonance imaging.

References:

1. Burns S, Harmel A, Miller S, et al. Clinical challenges of acute porphyria in the young adult. *Neurohospitalist*. 2022;12(2):377-382.

Once Suspected, Appropriate Testing Can Help Diagnose AHP^{1,2}

Diagnostic Workflow for AHP¹

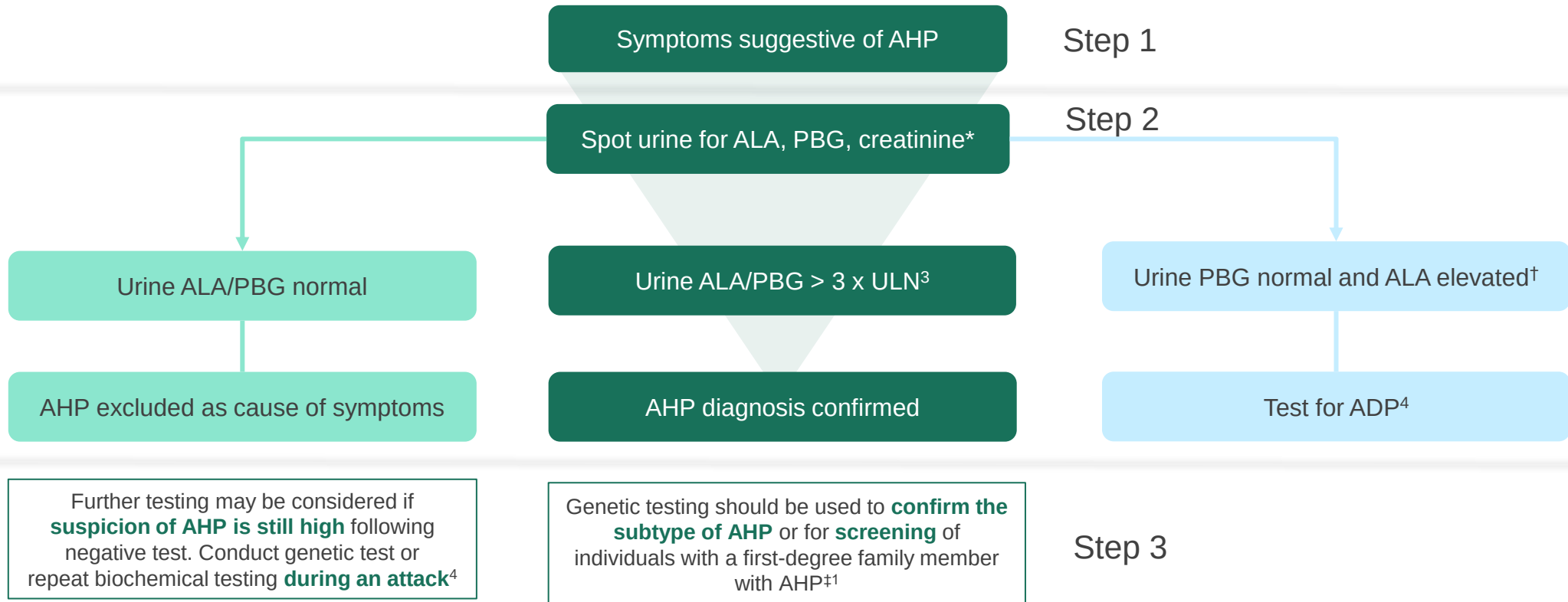


Figure adapted from Wang B et al. *Gastroenterology* 2023;164:484-491 and Moghe A et al. *Hepatology*. 2025;82:1603-1618.

*Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic.¹ [†]If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.^{1‡} Most carriers of pathogenic variant in AHP genes do not experience symptomatic acute attacks in their lifetimes. The phenotypic penetrance of symptomatic disease is approximately 1% of AHP gene carriers, with a penetrance of >20% in families with symptomatic patients. HCP and VP are reported to have lower penetrance than AHP.¹ ADP, aminolevulinic acid dehydratase deficient porphyria; AHP, acute hepatic porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; ULN, upper limit of normal. 1. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. *Gastroenterology*. 2023;164(3):484-491; 2. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment for the acute porphyrias. *Ann Intern Med* 2005;142:439-450; 3. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362(2):113-121; 4. Moghe A, McGuire BM, Levy C. Acute hepatic porphyrias-A guide for hepatologists. *Hepatology*. Published online April 12, 2024.

Summary

Abbreviations:

AHP, acute hepatic porphyria; GI, gastrointestinal; QoL, quality of life.

References:

1. Puy H, Deybach JC, Lamoril J, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet.* 1997;60:1373-1383;
2. Balwani M and Desnick RJ. The porphyrias: Advances in diagnosis and treatment. *Blood.* 2012;120:4496-4504;
3. Syed YY. Givosiran: A Review in Acute Hepatic Porphyria. *Drugs.* 2021;81:841-848;
4. Simon A, Pompilus F, Querbes W, et al. Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient.* 2018;11:527-537;
5. Schmolly K, Rudrapatna V, Beaven S. Recommendations for recognizing and diagnosing acute hepatic porphyria in atypical patient populations. *Orphanet J Rare Dis.* 2025;20(1):539;
6. Bissell DM, Lai JC, Meister RK, Blanc PD. Role of delta-aminolevulinic acid in the symptoms of acute porphyria. *Am J Med.* 2015;128:313-317;
7. Bissell DM, Anderson KE, Herbert L, et al. Porphyria. *N Engl J Med.* 2017;377:862-872;
8. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet.* 2015;8:201-214;
9. Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology.* 2020;71(5):1546-1558;
10. Wheeden K, Howe DL, Burrell S, et al. Patient perspective on acute hepatic porphyria with sporadic attacks: A chronic disease with substantial health-related quality of life impacts. *Adv Ther.* 2022;39:4330-4345;
11. Ko JJ, et al. Poster presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018: Philadelphia, PA;
12. Gerischer LM, Scheibe F, Nümann A, et al. Acute porphyrias – A neurological perspective. *Brain Behav.* 2021;11(11):e2389;
13. Li W, Lian ZY, Mi XJ, et al. Acute intermittent porphyria with epilepsy as the initial manifestation and posterior reversible encephalopathy syndrome: A case report. *Case Rep Neurol Med.* 2025;5596570;
14. Sharma SR, Sharma N, Synmon B, et al. Porphyria-induced Postpartum Reversible Posterior Encephalopathy Syndrome. *Indian J Crit Care Med.* 2022;26(6):728-730;
15. Theuriet J, Gerfaud-Valentin M, Durel CA, et al. Neuralgic amyotrophy presentation of acute intermittent porphyria: A case report. *J Peripher Nerv Syst.* 2024;29(4):567-569;
16. Jesuthasan A, Wride M, Esdaile H et al. An unexpected case of acute intermittent porphyria. *Acute Med.* 2024;23(1):46-49;
17. Indika NLR, Kesavan T, Dilanthi HW, et al. Many pitfalls in diagnosis of acute intermittent porphyria: A case report. *BMC Res Notes.* 2018;11(1):552;
18. Dukkipati SS, Terschluse J, Thodeson D, et al. Porphyric encephalopathy in a 15-year-old girl: A case report. *SAGE Open Med Case Rep.* 2025;13:2050313X24129853220;
19. Eroglu S, Birsenogul I. Delirium with delayed diagnosis of hereditary coproporphyria. *Clin Case Rep.* 2022;10(6):e05937;
20. Anderson KE, Desnick RJ, Stewart MF, et al. Acute hepatic porphyrias: 'Purple flags'-clinical features that should prompt specific diagnostic testing. *Am J Med Sci.* 2022;363(1):1-10.

