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Acute Intermittent Porphyria: A Neurological Dilemma Obscured by Ubiquitous Gastrointestinal Presentation

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Abstract
Acute intermittent porphyria (AIP) is a rare genetic hepatic porphyria that can progress to severe neurovisceral complications. Its early presentation commonly mimics benign gastrointestinal (GI) disorders, often leading to misdiagnosis and delayed treatment. This review highlights subtle early clinical features, emphasizes the importance of including AIP in differential diagnoses of unexplained abdominal pain, and integrates multi-systemic manifestations for early recognition. Several case reports demonstrate how misinterpretation of common, non-alarming symptoms can ultimately result in irreversible neurological injury. A single, widely available screening test—urinary porphobilinogen (PBG)—plays a crucial role in early detection. This review underscores the need for heightened clinical suspicion, early laboratory screening, and appropriate management to prevent complications.

Keywords*: Porphyria, neurovisceral symptoms, diagnostic delay, abdominal pain, urinary PBG, acute hepatic porphyrias.*

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I. Introduction

Acute intermittent porphyria (AIP) is a severe form of acute hepatic porphyria that presents infrequently but may become life-threatening if unrecognized. Due to its vague, multisystemic clinical profile and ability to mimic several common conditions, AIP is frequently misdiagnosed. Abdominal pain is the most common presenting symptom in outpatient settings; however, its nonspecific nature often leads clinicians toward gastrointestinal causes. By the time AIP is correctly diagnosed, neurological complications may have already progressed, highlighting the need for early recognition and prompt treatment to prevent irreversible nerve injury and mortality.[1]

II. Epidemiology and Clinical Spectrum

AIP results from mutations in the HMBS gene—over 391 variants have been identified—leading to accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). The global prevalence of acute porphyrias is approximately 5 per 10,000 population.[2]

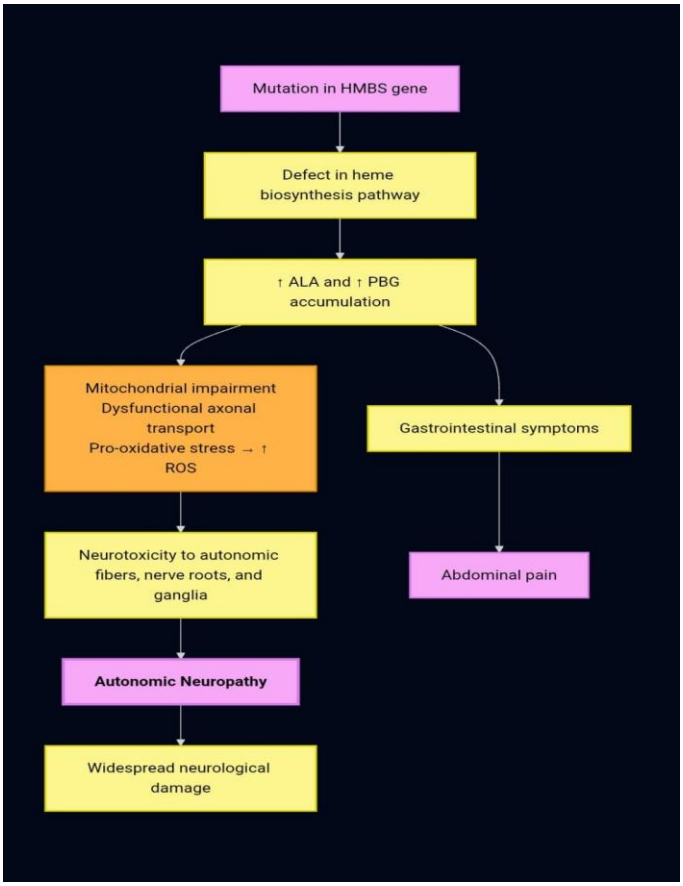
In India, AIP remains rare but shows clustering in certain communities, particularly the Maheshwari community of Bikaner, where prevalence is approximately 1 in 640 individuals.[3]

AIP is multifactorial, with numerous triggers precipitating symptomatic attacks, including:
excessive alcohol intake
fasting or crash dieting
psychological or physical stress
infections
hormonal factors
porphyrogenic drugs (e.g., ketamine, thiopental, chloramphenicol, rifampicin, valproic acid, carbamazepine, phenytoin, phenobarbital, spironolactone), as listed by NAPOS.[2]

Clinical features of acute attacks typically begin with severe abdominal pain—epigastric, colicky, and associated with nausea, vomiting, and constipation—followed by psychiatric symptoms and peripheral neuropathies.[2] The disease course is highly variable, and without timely diagnosis, can rapidly progress to life-threatening complications.

III. Pathophysiology of Abdominal Pain[19][20]

This Flowchart shows how the pathology of Porphyria gives the presentation of abdominal pain.



IV. Patterns of Misdiagnosis and Diagnostic Delay (Case Reports)

1. Misdiagnosed as Cholecystitis
A 26-year-old postpartum woman in the UK presented with severe abdominal pain interpreted as cholecystitis. She later developed seizures, hyponatremia, sinus tachycardia, and neuropsychiatric symptoms. Imaging showed contracted gallbladder with stones, but biochemical tests ultimately confirmed AIP.[4]

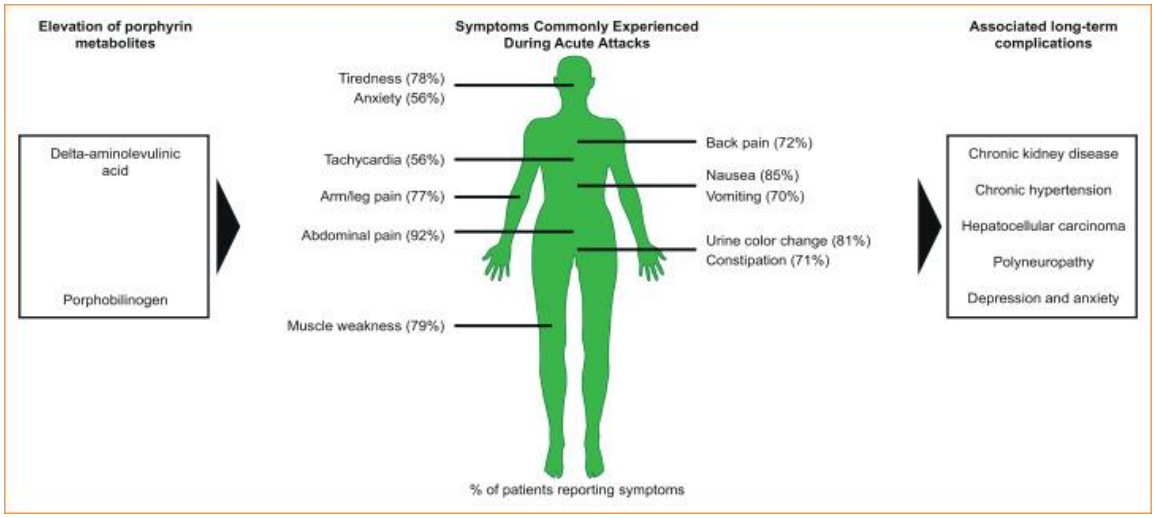
2. False Laparotomy Due to Suspected Appendicitis
A 16-year-old girl presenting with severe abdominal pain underwent multiple investigations (USG, CT, CSF, autoimmune panel), all normal. A laparotomy was performed unnecessarily, delaying diagnosis. She later developed seizures and neurological symptoms; AIP was confirmed through elevated urinary PBG levels.[5]

3. Porphyria Considered but Missed Due to Incorrect Screening
A 16-year-old boy with recurrent abdominal pain and psychiatric symptoms was repeatedly treated for presumed colitis. Though porphyria was suspected, an incorrect test led to delayed diagnosis.[6]
These cases highlight the need for greater awareness of AIP and appropriate diagnostic protocols.

V. Discussion

AIP is a metabolic disorder with vague, multisystemic symptoms. The nonspecific nature of abdominal pain frequently misleads clinicians toward more common gastrointestinal or surgical conditions. Case reviews demonstrate that early inclusion of AIP in differential diagnoses—particularly unexplained abdominal pain with neuropsychiatric features or SIADH—can significantly reduce diagnostic delays.[7–10] High clinical suspicion and awareness of early warning signs are essential for preventing severe complications.

Following chart is a reference from American Journal Of Medical Sciences showing abdominal pain as the most commonly appearing symptoms during Acute porphyric attacks and long term complications of it if disease is not managed and diagnosed in the early stage.[12]



VI. Strategies for Early Recognition

1. Education and Awareness
Greater clinical familiarity with rare disorders like AIP is essential to minimize diagnostic gaps and enable early management.

2. Diagnostic Algorithm
Diagnosis relies on:
detailed history
clinical suspicion
appropriate laboratory screening

First-line screening:
Urinary Porphobilinogen (PBG)
ALA levels (random urine sample, normalized to creatinine)[13]
Urinary porphyrins may be elevated but are non-specific.

Second-line testing:
Plasma porphyrins
Fecal porphyrins
Genetic analysis

3. Genetic Counseling
Genetic testing (ALAD, HMBS, CPOX, PPOX) helps confirm subtype and allows screening of at-risk family members.[11][12]

VII. Future Directions and Research

The rarity and complexity of AIP necessitate further research using animal models to understand pathophysiology and emerging therapies.[14] New biomarkers—such as CLEC10A, Neurofilament Light Chain (NfL), and markers of hepatic/renal injury (e.g., KIM-1, α-GST, FABP-1)—are being explored.[15–17]
AI-based human-in-the-loop decision support systems may improve early detection, but require validation.[18]

VIII. Conclusion

This review demonstrates how a seemingly common presentation—abdominal pain—may mask AIP, a rare but serious disease. High clinical suspicion, early urinary screening for PBG, and better awareness can break the pattern of diagnostic delay, reducing irreversible neurological complications and improving outcomes

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