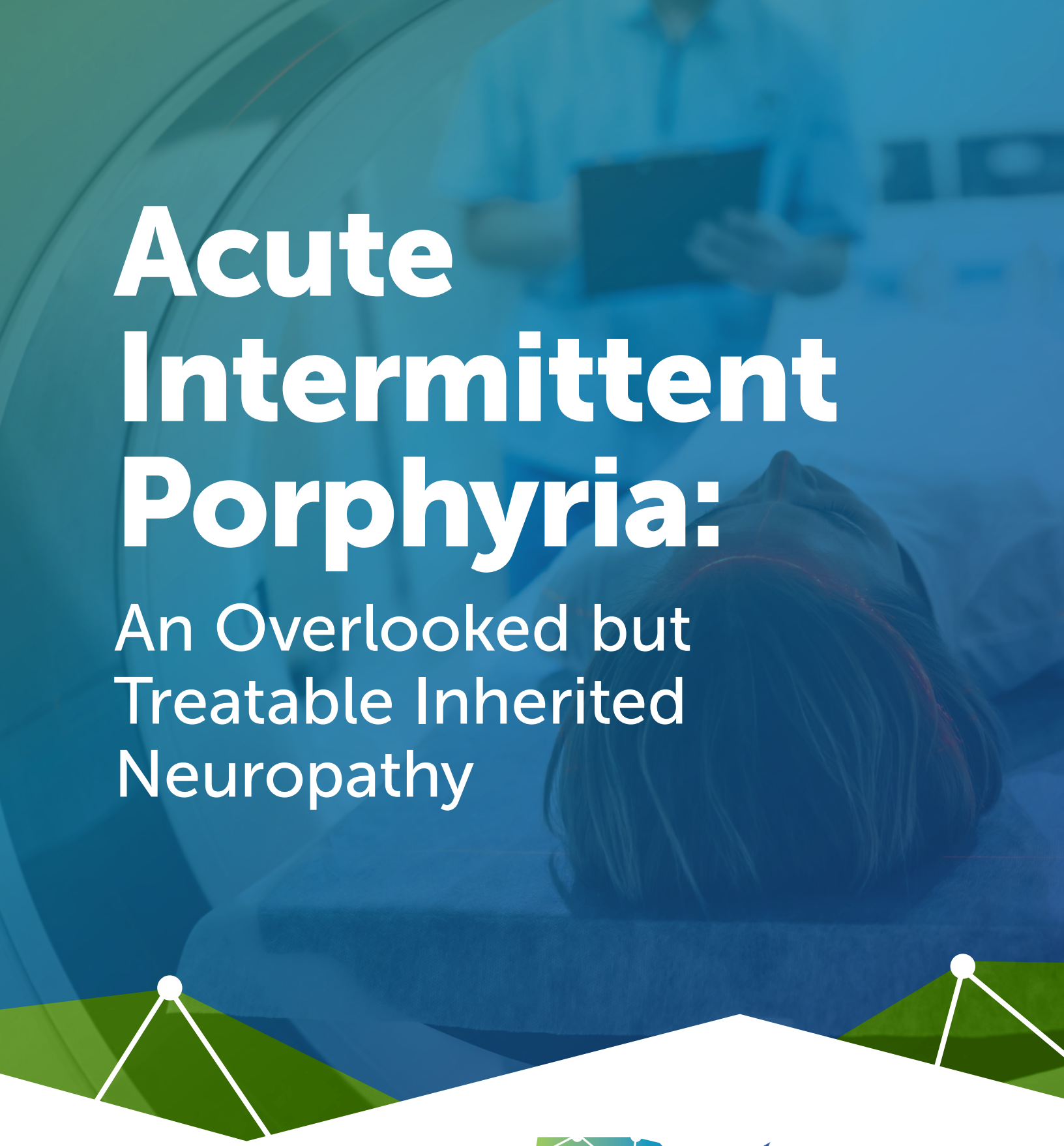
Acute Intermittent Porphyria:

An Overlooked but Treatable Inherited Neuropathy



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Clinical Neurological Society of America

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What is Acute Intermittent Porphyria?

Acute intermittent porphyria (AIP) is a rare genetic disorder resulting from the deficiency in one of the enzymes in the heme biosynthetic pathway, leading to the accumulation of neurotoxic heme precursors.[1] AIP is one of four acute hepatic porphyrias.

The disease is characterized by episodic attacks that typically feature autonomic, peripheral, and central system involvement. There can be significant residual neurologic manifestations in between the attacks in those with recurrent episodes. Delays in diagnosis and treatment can lead to significant neurologic disability over the years.

The most common symptoms and signs during an attack are unexplained, excruciating abdominal pain, nausea, vomiting, constipation, and pain in the arms, legs, or back.[2-4] People with AIP may also experience peripheral neuropathy, characterized by muscle weakness and generalized paresthesia (burning or tingling sensation often in the limbs), and/or encephalopathy with seizures, anxiety, insomnia, agitation, and altered consciousness.[5] Psychosis and delusions may also occur.

Autonomic manifestations during the attacks caused by involvement of the parasympathetic and sympathetic nervous systems can include resting and orthostatic tachycardia, systolic hypertension, and excess sweating, often without a fever.[6] A change in urine color is often seen, though is not specific to acute attacks. The acute abdominal pain is believed to be a manifestation of autonomic neuropathy. Patients do not typically experience all of these symptoms, and in fact the pattern of symptoms can vary substantially in different individuals.[3] These symptoms are nonspecific, and patients are often misdiagnosed.

> “Some patients can have an atypical presentation. For some, the main symptom is neuropathy, with a remote history of an acute attack that was not well defined.”
>
> **–Dr. Manisha Balwani**

FIGURE 1

Example symptoms experienced during acute attacks of AIP[2,3]

Underlying Genetic Cause

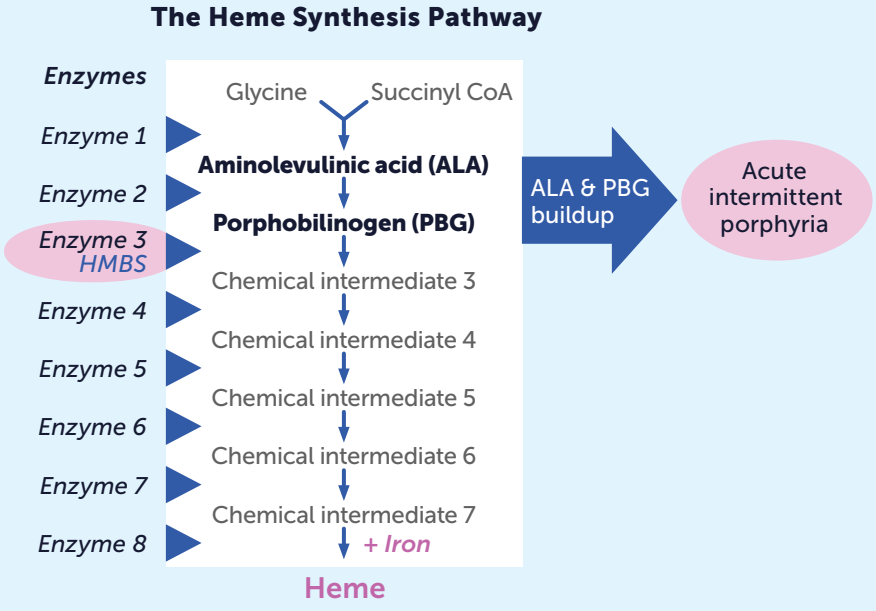
The underlying cause of AIP is a genetic mutation in the pathway used to synthesize heme. Heme is synthesized in eight steps. At each step a different enzyme enables a reaction that produces an intermediate chemical on the way to the final product, heme. In AIP, a mutation in the enzyme known as HMBS (hydroxymethylbilane synthase) decreases the enzyme's activity by about 50%.[7] In the liver, this can lead to a buildup of chemical intermediates in the heme pathway, which are known as ALA (aminolevulinic acid) and PBG (porphobilinogen), when heme demand is increased. ALA specifically is toxic to nerve cells. In AIP, the source of ALA and PBG buildup is the liver, which is a major site of heme synthesis.[8]

> "We think that ALA and PBG are neurotoxins. They can affect all types of nerves in the body, resulting in a wide range of symptoms."
>
> **–Dr. Bruce Wang**

FIGURE 2

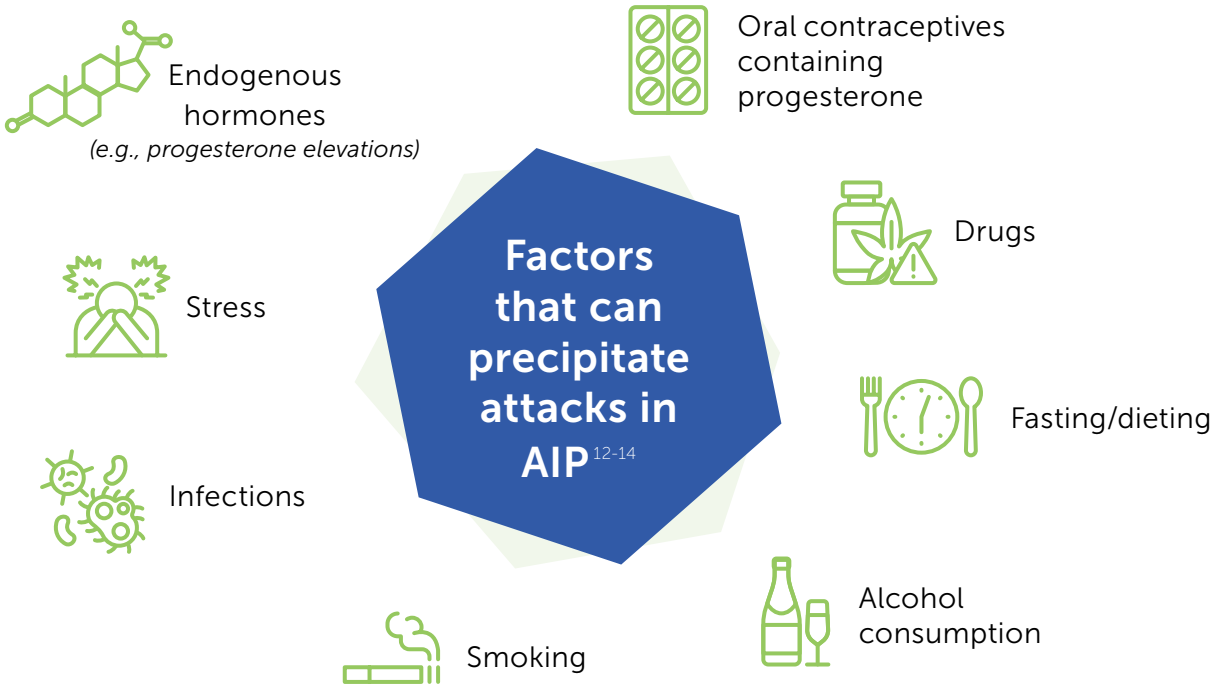
Pathophysiology of AIP

In AIP, the third enzyme in the heme synthesis pathway, HMBS (hydroxymethylbilane synthase), is decreased in activity due to a genetic mutation. This leads to a buildup of the chemical intermediates, ALA and PBG. ALA is primarily toxic to nerve cells.



Events that Precipitate Attacks

Acute attacks in AIP are often precipitated by internal or external factors that increase the liver's demand for heme which induce the rate limiting enzyme ALA synthase 1.[8] Such factors include hormones, stress, alcohol consumption, smoking, fasting, dieting, and infections (e.g., urinary tract infection,[9] COVID-19,[10] pyelonephritis,[11] gastroenteritis[11]).[12, 13] Some women may have cyclic attacks related to their menstrual cycle.[14] A variety of medications are also associated with attacks, including certain antibiotics, anticonvulsants, antitumor agents, antivirals, cardiovascular medications, and immune-targeting drugs.[14]



Epidemiology

AIP is classified as a rare disease based on the number of people who show symptoms—about six to 15 per 1 million based on studies in Europe, Australia, and Japan.[15, 16] However, many more people have disease-causing mutations in the HMBS gene but never develop the disease, or experience only mild symptoms that are overlooked.[2] Indeed, several studies have found that only about 1% of people in the general population with genetic mutations in the HMBS gene develop symptoms of AIP.[7, 17] In contrast, among people in families where at least one member has AIP, about 22% of those with the relevant mutations develop the disease. This has led experts to conclude that multiple genetic and environmental factors determine whether someone will develop symptoms,[7, 17] and research is underway to identify these factors.

Most patients who experience symptoms of AIP are female (up to 89%).[3, 18] Acute attacks in women typically begin after puberty and are less common after menopause.[19]

Burden of Disease and Long-Term Complications

AIP can have a significant negative impact on patients' quality of life. Lack of a diagnosis can be frustrating, as symptoms frequently mimic other conditions and may be discounted by others, including healthcare professionals, with some patients being labeled as drug seeking.[20]

The course of disease, and consequently the burden, is highly variable. Most people with genetic mutations in the HMBS gene never experience any acute attacks, and those who have acute attacks experience only one or two episodes in their lifetimes. A subset of patients has recurrent acute attacks (defined as four or more per year), with the average being six attacks per year.[3] However, even in this group the number of attacks per year is highly variable, with some reporting up to 50 attacks per year.[3]

Many people remain symptom free between attacks. However, among those who experience recurrent attacks, 65% report chronic symptoms,[3] including chronic pain, nausea, fatigue, and neuropathy (manifested as numbness and tingling).[19-21] In one study of people who had recurrent attacks, more than 60% reported pain between attacks.[3] In another study, 52% of 94 patients reported chronic symptoms, including nausea, fatigue, pain, neuropathy, and psychiatric disorders.[22] In these individuals, the disease worsened over time in the absence of appropriate treatment.

AIP may also be associated with damage to the central nervous system from seizures, coma, syndrome of inappropriate antidiuretic hormone (SIADH), and porphyria-induced posterior reversible encephalopathy syndrome (PRES).[16] Over the long term, AIP increases the risk of hypertension, chronic kidney disease, and liver cancer.[1]

FIGURE 3

Multiple disease manifestation patterns in AIP

Although everyone with AIP has a disease-associated mutation in the HMBS gene, the frequency of attacks, chronic effects, and long-term complications over the course of a lifetime vary considerably.

	Latent AIP	Sporadic AIP	Recurrent AIP
Frequency of acute attacks	No attacks during lifetime	A few sporadic attacks during lifetime	>4 per year; exact number highly variable
Chronic effects and long-term complications	Not well studied	Minimized if acute attacks treated promptly	Likely; may be minimized by prophylaxis and prompt treatment of acute attacks

Sequelae of AIP may include motor weakness or flaccid paralysis, which can lead to respiratory failure.[23] Sleep problems, including insomnia, are frequent features during acute attacks and chronically in patients with recurrent attacks.[3, 20]

Other chronic complications include chronic kidney disease; in one study of 55 patients, 14.5% had been diagnosed with chronic kidney disease at a mean age of 35 years,[24] whereas an earlier study found that 59% of 415 patients developed chronic kidney disease.[25] Without proper treatment, chronic kidney disease can progress to kidney failure, which requires lifelong kidney dialysis or kidney transplantation for survival.

Psychiatric symptoms, including anxiety, depression, delusions, and hallucinations can also significantly impact a person's life.[26] Although some may experience a mild form of "brain fog," others experience much more serious and pervasive neurocognitive dysfunction.

> "The cumulative toll this disease takes on higher brain function and memory can be substantial. This is not a benign condition."
>
> **–Dr. Richard Andrews**

> "Over time, neurologic deficits get worse and become more permanent rather than cyclical occurrences associated with acute attacks."
>
> **–Dr. Mohamed Kazamel**

AIP also negatively impacts employment. A small study of people with recurrent attacks found that 12 of 19 were unemployed and three additional people were employed only part time because of their disease, despite being of working age.[20] Lack of employment adversely affects finances, which is coupled with high medical bills.

Repeated medical visits and hospitalizations associated with AIP are extremely disruptive to people's lives. Recurrent attacks often last four to five days and require hospitalization.[20] In a medical records study of more than eight million people, those with AIP required a median of 23 physician visits in the year prior to diagnosis (vs. 16 in the general population) and 34% were hospitalized at least once during this period (vs. 19% in the general population).[27]

The economic costs of AIP are also substantial. The average total cost of care for patients with AIP in the United States who receive one of the two main recommended treatment options is estimated at $135,000 to $617,000 per patient per year.[28]

Diagnosis

As a rare disease with nonspecific symptoms, AIP is often missed or misdiagnosed. Patients often undergo numerous tests, many of which are negative. The key diagnostic test for AIP is urine porphobilinogen corrected to creatinine in a spot sample of urine.

> “It’s not just that physicians don’t consider AIP as a diagnosis. It’s also that they order incorrect tests.”
>
> **–Dr. Rachana K. Gandhi Mehta**

Historically, patients reported a delay of up to 15 years or more before they obtained a diagnosis.[19] The availability of genetic tests is expected to reduce this delay and use of machine learning may help reduce it further, with one study finding that such an approach may improve time to diagnosis by 1.2 years.[29]

> “It’s worth noting that inherent to delayed diagnosis is often a multitude of tests, such as abdominal and GI imaging and neuropsychological assessments, that may lead to unhelpful treatments.”
>
> **–Dr. Eddy Lang**

A long list of differential diagnoses is available considering the numerous symptoms of AIP. Severe abdominal pain may be caused by peritonitis, appendicitis, acute cholecystitis, endometriosis, ovarian cysts, and many other conditions.[30] Abdominal pain in AIP is very severe and increases over a few days. The diagnosis should be considered in patients who have frequent abdominal pain accompanied by a normal work-up or who have been referred to pain clinics for chronic abdominal pain.

> This disease is often misdiagnosed as Crohn's disease or inflammatory bowel disease or written off as musculoskeletal pain, which often translates as malingering or attention seeking behavior.

–Dr. Richard Andrews

Autonomic neuropathy, another frequent symptom of AIP, also has many potential causes, including hypertensive crisis, adrenal crisis, tachyarrhythmias, Guillain-Barre syndrome, botulism, and others.[30] A key to diagnosing AIP is that patients often present with acute abdominal pain plus another symptom such as weakness or neuropathy that would suggest a neurology consultation.

> We sometimes see patients diagnosed because the neurologist requested genetic testing such as a multi-gene panel for neuropathy, and HMBS was one of the genes included.

–Dr. Manisha Balwani

Possible causes of psychiatric symptoms include an acute psychotic episode, delirium, and panic attack.[30]

Patients who experience severe attacks of AIP nearly always visit the emergency department at some point in their disease. However, patients are very rarely diagnosed at an emergency visit during an acute attack when their levels of ALA and PBG are high because these results typically take a few days to come back and so are typically not ordered during the visit.

> After multiple emergency visits and numerous tests have shown nothing, a pattern begins to emerge and the astute physician, willing to take a fresh look, will refer the patient for proper testing or even get them admitted for a work-up of abdominal pain. This is the way a diagnosis gets made.

–Dr. Eddy Lang

According to expert advice, AIP should be considered in women aged 15-50 years who present with unexplained, severe abdominal pain without a clear cause after an initial workup.[31, 32] Diagnosis should be based on high levels of PBG and ALA in the urine, which are elevated to at least five-fold normal values or > 10 mg/g creatinine during acute attacks.[1] Once high levels of these chemicals in the urine have been confirmed, genetic testing can be done to determine the specific type of acute hepatic porphyria, of which AIP is the most common.

Barriers to Diagnosis

A number of barriers influence the diagnosis of AIP.

Rarity of the disease. Due to the rarity of symptomatic AIP, physicians do not expect to see it and do not think about it as a diagnosis.

> "Physicians often learn about this disease in medical school and then it is not on their radar after that."
>
> **–Dr. Mohamed Kazamel**

Misinterpretation of symptoms. Many symptoms of AIP can be mistaken for other disorders. For instance, patients may be referred to pain management clinics for their pain or diagnosed with Guillain-Barre syndrome because of the acute onset weakness.[33]

> "In patients who present with acute/subacute neuropathy along with abdominal pain, mental status changes, or seizures and lack of demyelinating changes, AIP should be considered."
>
> **–Dr. Rachana K. Gandhi Mehta**

Lack of readily available biochemical testing. Tests for the initial screening of AIP are often unavailable in house and samples are typically sent out for testing; however, the tests are often not ordered or the sample is inappropriately exposed to light during handling and shipment.

The need for genetic testing. Genetic testing for AIP is not always performed even though it is available through a sponsored testing program in the United States and Canada.[34]

Treatment and Management

An important first point in the management of AIP is the avoidance of factors known to trigger acute attacks. These include certain medications, steroid hormones (especially progesterone), alcohol, tobacco use, physical or psychological stress, and nutritional changes such as dieting.[1] People with AIP can help manage their condition by diligently avoiding triggers and ensuring that they have a care plan in their medical file that they can present to the emergency professionals in case of an attack.

Acute attacks of AIP should be managed with intravenous hemin. Intravenous hemin reduces pathway activation in the liver and shuts off overproduction of ALA and PBG.[35] Hospital pharmacies should keep a supply of hemin available at all times for patients with AIP.

> "The earlier you treat, the better the outcomes because delays in treatment lead to chronic complications."
>
> **–Dr. Manisha Balwani**

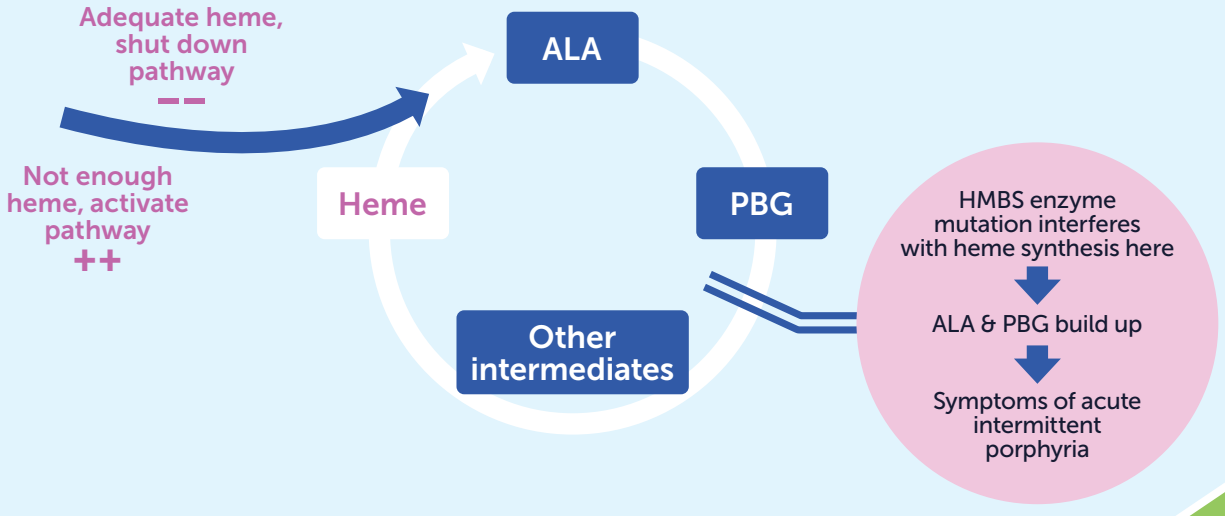
Patients should also be given pain medications, antiemetics, and treatment for systemic arterial hypertension, tachycardia, and hyponatremia and hypomagnesemia (if present).[1]

Hospitalization is often required for treatment of acute attacks.[35] Acute attacks should be treated with daily intravenous hemin, usually for four days.[1] This allows time for reduction of ALA and PBG and an improvement in symptoms.

FIGURE 5

Hemin acts to restore heme balance and reduce activation of the heme synthesis pathway.

This reduces overproduction of ALA and PBG.[35]



Patients vary in their recovery from an acute attack and some patients may require a rehabilitation plan.[23] Ideally, rehabilitation is supported by a multidisciplinary team that includes a neurologist, physical therapist, occupational therapist, speech therapist, nutritionist, and psychologist.[23]

A multidisciplinary team of physicians is also important for managing acute and long-term complications. AIP increases the risk of kidney and liver diseases and may also entail pain management and psychiatric treatment, so specialists in these areas often work together.

Patients who experience recurrent attacks of AIP should be considered for prophylactic heme therapy or givosiran, a small interfering RNA (siRNA) that suppresses the production of ALA.[1, 6]

Unfortunately, hemin and givosiran are not readily accessible to all patients, even in the United States. Prophylactic treatment with hemin can reduce costs compared with acute treatment.[36]

> “With the availability of disease-modifying treatment, the natural history of AIP has shifted somewhat toward a chronic condition rather than repeated attacks.”
>
> **–Dr. Mohamed Kazamel**

Patients with significantly decreased quality of life whose symptoms are not controlled by pharmacotherapy may be considered for liver transplantation.[1]

Historically, carbohydrate loading with glucose has been used to treat acute attacks. However, this should not replace IV hemin. Many patients start to increase their carbohydrate oral intake once they feel that they are about to go through an attack. The effectiveness of this practice has not been proven.

Summary

Acute intermittent porphyria is a rare, inherited disease characterized by acute symptomatic attacks that may involve all levels of the nervous system. The most common symptom is severe, unexplained abdominal pain that increases over a few days, often accompanied by discolored urine or various neurological or psychiatric signs or symptoms. Chronic complications are frequent and a long-term individualized management plan by a multidisciplinary team is indicated to help monitor and address such complications. Diagnosis of AIP is frequently missed due to the rarity of the disease, misinterpretation/misdiagnosis of symptoms, and lack of readily available testing. It is imperative to improve our methods of diagnosing AIP, as several effective treatments are available that can substantially improve patients’ lives.

CNSA's Clinical Proceedings

The Clinical Neurological Society of America has more than 50 years of experience bringing together leading experts and clinical neurologists for educational programming. CNSA's Clinical Proceedings—a white paper series—are informational resources intended to raise awareness and address unmet needs in neurology. CNSA recognizes the expert panel members who contributed to the development of this white paper.

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Rachana K. Gandhi Mehta, MD, MBBS

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