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Acute Hepatic Porphyrias

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Declaração de Integridade

Eu, Inês Correia Marques, que abaixo assino, estudante com o número de inscrição 44147 do curso de Medicina da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Universidade da Beira Interior, Covilhã 27 /01 /2025

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(a44147)

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Abstract

Introduction: Porphyrias are rare genetic disorders caused by heme biosynthesis pathway enzyme mutations, leading to porphyrin precursors build up in various tissues and diverse symptoms. This review centers on acute hepatic porphyrias (AHP).

Methods: A MEDLINE via Pubmed database literature review was conducted. Systematic reviews, clinical trials, cohort studies, case-control studies, expert reviews, and guidelines were preferred for analysis.

Results: There are four types of AHP: acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and δ-aminolevulinic acid dehydratase deficiency porphyria. These conditions primarily present as neurovisceral attacks, characterized by severe abdominal pain, neuropsychiatric symptoms or skin lesions, predominantly affecting women aged 15 to 50. The diagnostic methods include biochemical tests that assess urinary levels of aminolevulinic acid and porphobilinogen. Additionally, measuring porphyrin levels in urine or feces can provide more insights into the type of AHP; however, a definitive diagnosis of the specific type is made through genetic testing. Treatment involves high-glucose diets, intravenous hemin for acute attacks, and givosiran for the prophylaxis of frequent attacks. Liver transplantation remains the only curative option. It is crucial to monitor chronic complications associated with hepatic porphyrias, particularly hepatocellular carcinoma, kidney disease, and arterial hypertension.

Conclusion: AHP continues to be an underrecognized condition, warranting consideration in individuals experiencing unexplained abdominal pain, neuropathy, psychiatric symptoms, or skin lesions. There is a need for improved diagnostic techniques and treatment options.

Keywords

Porphyrias; acute hepatic porphyrias; heme; liver; hemin.

Resumo

Introdução: As porfirias são doenças genéticas raras causadas por mutações em enzimas responsáveis pela biossíntese do heme, levando à acumulação de precursores de porfirinas em vários tecidos e manifestação de diversos sintomas. Esta revisão foca-se nas porfirias hepáticas agudas (AHP).

Métodos: Foi realizada uma revisão da literatura na base de dados MEDLINE via PubMed. Revisões sistemáticas, ensaios clínicos, estudos de coorte, estudos caso-controlo, revisões por *experts* e *guidelines* foram priorizadas para análise.

Resultados: Existem quatro tipos de porfirias hepáticas agudas: porfiria aguda intermitente, porfiria variegata, coproporfiria hereditária e porfiria por deficiência de ácido δ- aminolevulínico desidratase. Estas patologias manifestam-se principalmente como crises neurovisceral, nomeadamente por dor abdominal intensa e sintomas neuropsiquiátricos, afetando sobretudo mulheres entre os 15 e os 50 anos de idade. O diagnóstico baseia-se em testes bioquímicos de urina que doseiem os níveis de ácido aminolevulínico e porfobilinogénio. Além disso, os níveis de porfirinas na urina ou nas fezes podem ajudar a definir o subtipo de AHP, mas o diagnóstico definitivo do subtipo só é possível por teste genético. O tratamento inclui a administração de hidratos de carbono, hemina intravenosa nas agudizações e givosiran para profilaxia de agudizações recorrentes. O transplante hepático é a única opção curativa. Doentes com AHP apresentam risco aumentado para carcinoma hepatocelular, doença renal crónica e hipertensão arterial.

Conclusão: As AHP continuam a ser uma patologia esquecida, devendo ser sempre um diagnóstico a considerar em doentes com dor abdominal idiopática, neuropatia, sintomas psiquiátricos, ou lesões cutâneas. São necessários melhores métodos diagnósticos e tratamentos para este grupo de patologias.

Palavras-chave

Porfirias; porfirias hepáticas agudas; heme; fígado; hemina.

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Abbreviations List

ADP	δ-Aminolevulinic Acid Dehydratase Deficiency Porphyria
AHP	Acute Hepatic Porphyria
AIP	Acute Intermittent Porphyria
ALA	δ -Aminolevulinic Acid
ALAD	δ-Aminolevulinic Acid Dehydratase
ALAS	δ -Aminolevulinic Acid Synthase
ASHE	Asymptomatic High Excreters
CEP	Congenital Erythropoietic Porphyria
COPRO I	Coproporphyrin I
COPRO III	Coproporphyrin III
CPOX	Coproporphyrinogen III Oxidase
CYP 450	Cytochrome P450
DNA	Desoxyribonucleic Acid
EPP	Erythropoietic Protoporphyria
GnRH	Gonadotropin-Releasing Hormone
HCP	Hereditary Coproporphyria
HMBS	Hydroxymethylbilane Synthase
mRNA	Messenger Ribonucleic Acid
PBG	Porphobilinogen
PCT	Porphyria Cutanea Tarda
PPOX	Protoporphyrinogen Oxidase
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
siRNA	Small Interference RNA
VP	Variegate Porphyria
XLP	X-linked Protoporphyria

Introduction

Porphyrias are rare metabolic disorders resulting from genetic mutations in heme biosynthesis enzymes, accumulating porphyrins or their precursors in areas like bone marrow, skin, liver, and blood, which causes the symptoms (1–4).

The first porphyria case was described in 1870 (5). The heme biosynthesis pathway was discovered in 1945, followed by porphyrin separation in 1961 and the cloning of heme biosynthesis genes in 2000 (5).

There are eight types of porphyrias: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), δ-aminolevulinic acid dehydratase deficiency porphyria (ADP), erythropoietic protoporphyria (EPP), X-linked protoporphyria (XLP), porphyria cutanea tarda (PCT), and congenital erythropoietic porphyria (CEP) (1,6).

Porphyrias can be classified into erythropoietic and hepatic groups, depending on the site of precursor accumulation (7). They can also be grouped into cutaneous (PCT, CEP, EPP, and XLP) and acute hepatic types (AIP, HCP, VP, and ADP) based on their symptoms (7). The acute hepatic porphyrias (AHP) present with nonspecific symptoms, primarily abdominal pain, peripheral neuropathy, and psychiatric symptoms (Table 1) (2).

AHP affects approximately 5 in 100,000 people worldwide (8). AIP is the most common, with a prevalence of about 1 in 1,700 persons and an incidence rate of 0.13 new cases per one million persons-year (6,8). Of all the porphyrias, ADP is the least common, with only 9 cases described so far (6).

This review explores the clinical presentation, diagnosis, treatment, and prospects of AHP, a frequently overlooked condition with a challenging diagnosis due to its nonspecific symptoms. The review was carried out using MEDLINE via the PubMed database. The search query for PubMed was: ((Heme) AND (Biosynthesis) AND (Porphyrias)) OR ((Hepatic porphyrias) AND ((Diagnosis) OR (Treatment) OR (Prognosis) OR (Clinical manifestations)) OR (Porphyrias) OR ((Coproporphyria, Hereditary) OR (Porphyria, Variegate) OR (Porphyria, Acute Intermittent) OR (Aminolevulinate Dehydratase Deficiency Porphyria)). The research was limited to English, Spanish, or Portuguese articles, and no time restriction was made. Preference was given to systematic reviews, randomized controlled trials, cohort studies, case-control studies, expert reviews, and guidelines. The articles were selected and included based on the title and abstract.

Pathophysiology

Heme, a porphyrin ring bound to ferrous iron, is a crucial prosthetic group in proteins like hemoglobin and myoglobin, and supports enzymes such as cytochromes, catalase, and nitric oxide synthase (9). It can be synthesized in all human cells (3). However, the majority is produced in bone marrow (75 to 80%) and a smaller amount in hepatocytes (15 to 20%) (4,10,11).

The first step in heme biosynthesis is the formation of δ-aminolevulinic acid (ALA) by the condensation of glycine and succinyl-CoA through the action of the enzyme δ-aminolevulinic acid synthase (ALAS) (12). Two types of δ-aminolevulinic acid synthase are present: δ-aminolevulinic acid synthase 1 (ALAS1) and 2 (ALAS2). ALAS1 is the rate-limiting enzyme of heme biosynthesis in non-erythroid cells, such as hepatocytes, where the heme exerts negative feedback, causing a decreasing production of ALAS (11,13). Some precipitant factors have been described to upregulate δ-aminolevulinic synthase, such as drugs and hormones that induce cytochrome P 450. Following ALA formation, six other enzymatic reactions transform ALA into protoporphyrin IX (12). The last reaction in heme biosynthesis involves ferrochelatase, which catalyzes the attachment of ferrous iron to protoporphyrin IX, resulting in the formation of heme (12).

In cases of enzymatic deficiencies, specific heme precursors accumulate, depending on which step is affected (Figure 1) (12). In AHP, ALA levels are substantially elevated during attacks for all four types of AHP, while porphobilinogen is elevated for only the three most common forms (excluding ADP) (2,3,14,15). Studies show that ALA is primarily neurotoxic and responsible for neurovisceral attacks (10). In some AHP, the accumulation of porphyrins such as coproporphyrin III and protoporphyrin IX are photosensitizers and cause skin lesions (Figure 1) (10).

AIP, HCP, and VP have a dominant inherence and result, respectively from mutations in hydroxymethylbilane synthase (HMBS), protoporphyrinogen oxidase (PPOX), and coproporphyrinogen III oxidase (CPOX) alleles, and respective enzymatic deficiencies (Figure 1 and Table 1) (12). ADP has an autosomal recessive inherence and results from a mutation in δ-aminolevulinic acid dehydratase (ALAD) allele, leading to a reduction in the activity of this enzyme (Figure 1) (12).

AHP have low penetrance for patients with clinically relevant mutations, so most patients generally exhibit low clinical manifestations, with few or no attacks during their lives (1,6,8).

Clinical Manifestations

Most of the symptomatic AHP patients have neurovisceral attacks, marked by severe abdominal diffuse colicky pain, often accompanied by nausea, vomiting, hyponatremia, hypertension, tachycardia, constipation, and dark urine (2–4,8,16,17). Severe abdominal pain occurs in 74-100% of cases and lasts from hours to several days (8,16). Despite intense abdominal pain, physical examination often reveals no focal abnormalities or rigidity (2–4,8,16,17).

Neuropsychiatric symptoms are also a possible manifestation and can occur before or during an acute attack (18,19). Seizures are other possible manifestation, and about 20-58% of patients can have anxiety, behavioral changes, sleep disturbances, psychosis, memory loss, depression, hallucinations, and delirium (8,18). Other features were also described as neuropathic pain and sensory loss (2). Typically, the development of peripheral neurological findings follows acute attacks in some days or weeks and includes progressive muscle weakness, starting proximally in the limbs (19). Other sensory symptoms may also occur, such as paresthesia, dysesthesia, and sensory loss in a "stocking-glove" distribution (2,8,19).

Hyponatremia is a frequent sign in AHP and a marker of acute attack severity (20). A few mechanisms have been described, but some studies relate the syndrome of inappropriate antidiuretic hormone secretion (SIADH) to this electrolyte disturbance (20). So, mental state alteration, delirium, seizures, and coma can occur due to hyponatremia but also secondary to an acute attack (8,19,20).

Acute episodes occur approximately four times more frequently in women than in men and can be triggered by various factors: sex hormones, medications that induce cytochrome P450 (barbiturates, anti-epileptics, sulfonamides, estrogen, progesterone, anesthetic agents, antidepressants, prokinetic and antiemetic drugs), acute illness, physical or psychological stress, alcohol, tobacco, pregnancy, and caloric restriction (2,8,13,16). Some women experience more manifestations during the luteal phase of their menstrual cycle because of the progesterone peak. Between 65-80% of patients have clinically latent disease (2,8,13,16).

The clinical presentation of AHP subtypes varies. ADP is the rarest AHP and is characterized by a more severe clinical presentation with recurrent neurological attacks, which can be life-threatening (15). AIP, the most common type, typically presents with prolonged autonomic disturbances or psychiatric symptoms lasting weeks, along with a higher prevalence of chronic issues like pain, nausea, fatigue, and neuropathic features (21). HCP and VP produce neurological symptoms similar to AIP, but the major distinct signs are cutaneous lesions, like blistering lesions in sun-exposed areas, milia, scarring,

thickening, facial hypertrichosis, and decreased or increased skin pigmentation (16,22). These cutaneous manifestations are more common in VP (12).

Most people with AHP become symptom-free between attacks, but patients suffering from frequent, recurrent attacks have a higher prevalence of chronic symptoms (8,18,23). Studies show that the most frequent chronic symptoms are abdominal pain, myalgias, muscle weakness, nausea, fatigue, insomnia, anxiety, and sleeping disorders (8,18,23). It is essential to highlight that AHP patients are at a higher risk for developing hepatocellular carcinoma, hypertension, and chronic kidney disease (4,8,24).

Diagnosis

There is a symptomatic triad consisting of severe abdominal pain, peripheral neuropathy, and involvement of the central or autonomic nervous system that should be assessed for the possibility of AHP when no other diagnosis can explain the clinical presentation (8). Early diagnosis enables prompt treatment of AHP, which can reduce morbidity and mortality (13).

The first-line diagnostic approach is the same for all AHP and includes screening of porphobilinogen and ALA in urine, usually positive when an acute attack is present (Figure 2) (2,4,8,13,14,17,25). A timely urine sample collection is recommended, especially during an acute attack or right after, and the urine is often red, purple, or brown (8). The Hoesch test using Ehrlich reagent is the most commonly employed qualitative test for porphobilinogen, known for its rapid results and availability in most emergency rooms (6,25). It is considered positive if urine turns red (6,25). However, some studies have indicated that the test has low sensitivity and specificity and does not measure ALA levels, which means it may overlook ADP (6,25).

The hallmark of AHP is the presence of elevated levels of porphobilinogen and/or ALA in urine (4,8). These levels should be quantified and normalized to creatinine excretion to account for any potential renal function impairment (4,8). Urinary levels of porphobilinogen and/or ALA above 10 mg/g creatinine are highly specific for diagnosing AHP, as normal levels are typically below 2-4 mg/g creatinine (Figure 2) (4). If porphobilinogen levels in urine are normal, and high suspicion of AHP is maintained, ALA levels in urine should be accessed because isolated ALA elevation should be differentiated between ADP and other causes unrelated to porphyrias, for instance, lead poisoning and hereditary tyrosinemia type 1 (26).

Porphobilinogen and ALA levels can stay elevated for months to years after an acute AIP attack but drop quickly after HCP or VP attacks. Therefore, measuring urine porphyrin levels is crucial to avoid misdiagnosing VP or HCP (4). However, isolated

elevations of urinary porphyrins do not suggest AHP and may occur in cases of secondary porphyrinuria (in hepatobiliary diseases, alcohol use, or cytochrome P450-inducing drugs intake) (2,4,11).

Second-line testing is important to define the subtype of AHP and includes plasma and fecal porphyrins and plasma fluorescence (2,4,8). On HCP, the levels of coproporphyrins in stool are higher than those of protoporphyrins, and coproporphyrin III (COPRO III) should comprise about 60-95% of the total coproporphyrin, with a ratio of coproporphyrin III to coproporphyrin I greater than 2 (Figure 3). (8,16). The most sensitive test to identify VP is fluorescent plasma scanning, which detects a characteristic fluorescence peak at a wavelength of approximately 626 nm of porphobilinogen (2,4,8). Additionally, both coproporphyrin and protoporphyrinogen levels are elevated (Figure 3) (2,4,8). ADP and AIP can have normal or slightly elevated levels of fecal porphyrins (2,4,8).

The definitive diagnosis requires desoxyribonucleic acid (DNA) analysis (2,4,8). A multigene panel is recommended and includes genes of interest such as PPOX, HMBS, CPOX, and ALAD (4,8,12,24). The use of a multigene panel allows the identification of the responsible mutation and the screening of other family members (11). However, sometimes, genetic testing might miss mutations in individuals with suggestive biochemical profiles or detect variants of uncertain significance, making clinical management difficult (11).

Diagnosing AHP is challenging due to their rarity, nonspecific symptoms, and diagnostic limitations. Triggers or family history are not always present and should not exclude the diagnosis, as sporadic mutations can occur (11).

When blistering lesions are seen, the first clinical suspicion is porphyria cutanea tarda (1,11,12,17). However, VP and HCP can also have this presentation, and they need to be considered to avoid misdiagnosis (11).

The limited availability of rapid urinary qualitative tests and the delayed results (1 to 2 weeks) for quantitative tests further complicate timely diagnosis (11). In VP, plasma fluorescence at 626 nm can help, but its availability is also restricted (11).

Management

Acute attack treatment

The treatment of acute neurovisceral attacks has two main goals: reduce ALAS1 expression in the liver and treat present symptoms (8,10). It is essential to be promptly initiated, even if empirically, because acute attacks can progress into severe and potentially life-threatening outcomes. Patients should be aware of the triggering factors described above and minimize or avoid them (2,16).

If mild symptoms are present, such as mild pain without other severe symptoms, the first approach should be an oral high-carbohydrate diet providing 55 to 60% of total caloric intake (4,8,27). If not well tolerated, carbohydrates can be administered intravenously as 5% dextrose in normal saline, with a maximum of 2 liters per day (8). However, electrolytes should be monitored because hyponatremia may worsen (2,4,13).

If mild symptoms do not improve, or if the condition is more severe - marked by intense abdominal pain, significant hyponatremia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, or arrhythmias - then a more aggressive treatment approach is necessary (8,14).

Hemin is the primary approved treatment, typically administered at a dosage of 3-4 mg/kg of body weight, once daily for 4 days up to 250 mg per day (8,14,28). It should be administered through a large venous peripheral catheter and combined with human serum albumin to minimize vein damage and decrease the risk of thrombophlebitis (2,4,16). The 350 mg hemin vial should be diluted in 147 mL of 25% human serum albumin, and the appropriate hemin-albumin solution volume should be administered based on the patient's weight (16). This improves the symptoms and prevents long-term neurological complications (2,16). If hemin is unavailable, administering 10–20% glucose in normal saline intravenously, at a dose of up to 2 liters per day, is recommended (8).

Effective pain management is essential for patient comfort: acetaminophen and non-steroidal anti-inflammatories (ibuprofen and naproxen) are the first-line drugs for mild pain and morphine for severe pain (2,8,14,29). Nausea and vomiting should be aggressively treated with antiemetics like ondansetron, chlorpromazine, or promethazine (8,13,29). Constipation can be present, and lactulose is usually effective (2,16). For seizures, a safe option is benzodiazepines since most antiepileptic drugs are not safe for patients with porphyria (8,29). Hyponatremia is mainly associated with SIADH and should be treated according to specific guidelines (8,13,19,20).

Usually, symptoms improve after the treatment of an acute attack. However, some patients continue to experience chronic symptoms, such as anxiety, hypertension,

insomnia, neuropathic pain, and muscle weakness or paralysis (8,23,24). These chronic symptoms should be addressed according to general treatment recommendations and by considering the safest medication options for patients with AHP (8).

Patients who are asymptomatic high excreters (ASHE) exhibit elevated levels of ALA and porphobilinogen despite not showing any symptoms (24). Treatment is not required unless they develop symptoms, despite limited data to prove this (24). However, they need to take preventive measures, such as avoiding known triggers, to reduce the risk of developing symptomatic porphyria (24).

Treatment of recurrent attacks

Recurrent attacks are defined as four or more acute attacks in the past year following one to two years of standard treatment (30). When these occur, off-label use of prophylactic hemin (3 mg/kg body weight, administered once per week) may be considered, even though its effects are not well documented (30). There is limited data on the safety and efficacy of hemin. Still, some studies suggest that it is safe for use during acute attacks and as prophylactic therapy, and it reduces the manifestations of acute hepatic porphyria with demonstrated efficacy (31–33). However, repeated use of hemin is associated with dependence on exogenous heme and side effects, including thrombophlebitis, coagulation abnormalities, and secondary iron overload (31,32,34,35). Patients relate these side effects with a poorer perceived health-related quality of life along with frequent health care interventions like regular infusions, psychological impact, and social limitations (34,36). Some studies also show that hemin prophylaxis has no effect on chronic symptoms between attacks, hence the need to explore alternative therapies (34,36).

Gonadotropin-releasing hormone (GnRH) analogs may be beneficial for cases of symptoms related to menstrual cycles because they inhibit sex hormones and reduce the progesterone peak, which is known to trigger attacks of AHP (2,4,8,16,24). However, a significant side effect of these analogs is estrogen deficiency, which can limit their use (2,14,16).

Givosiran is a small interfering RNA (siRNA) specifically targeting ALAS1. When given subcutaneously at a dose of 2.5 mg/kg once a month, it is selectively absorbed by hepatocytes, where it binds to ALAS1 messenger RNA (mRNA). This action leads to the degradation of ALAS1 mRNA, ultimately lowering ALAS1 expression (8,37). When recurrence occurs, givosiran can be given to patients aged 12 years and older with biochemically and genetically confirmed acute hepatic porphyria, lowering the levels of ALA and porphobilinogen while reducing the frequency of acute attacks (8,37). The use of prophylactic givosiran in patients with AHP and recurrent attacks has resulted in

reduced frequency of attacks, decreased reliance on hemin over time, and improved patient quality of life (34,36). This was attributed to less daily pain, reduced opioid use, enhanced daily activities, and alleviation of chronic symptoms between attacks (34,36). While it is deemed safe and approved, there is a possibility of adverse events, which may include higher blood homocysteine levels, increased transaminases, retinal vein occlusion, injection-site reactions, pancreatitis, deterioration of chronic renal failure, pulmonary embolism, right iliac thrombophlebitis, and worsening liver test results (31).

Liver transplantation is regarded as the only curative option for patients who do not respond to pharmacological treatment, and after the transplant, the levels of ALA and porphobilinogen return to normal (4,8,24,31). There is a low risk of disease recurrence after the liver transplant (4,8,38). Neurological acute symptoms, such as motor weakness or pain, may lessen; however, chronic neurological symptoms, like quadriplegia or paraplegia, show minimal improvement, with some patients experiencing little to no change (4).

Follow-up

AHP clinical monitoring should comprise symptom review, physical exam, medication assessment, and quality of life evaluation (8,24). This should take place every six months for sporadic attacks and every three months for recurrent attacks (8). Laboratory monitoring includes measuring urine levels of ALA and porphobilinogen, along with standard blood tests at each visit (8). These blood tests include a complete blood count and a metabolic panel, which consists of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, albumin, urea, creatinine, and electrolytes (8). Annual plasma alpha-fetoprotein level measures are recommended for all patients with AHP due to the increased risk of hepatocellular carcinoma (8). It is advisable to monitor plasma homocysteine levels since elevated levels correlate with disease activity, which may include symptoms or elevated ALA and/or porphobilinogen levels (8,39).

Moreover, patients experience a higher incidence of chronic kidney, liver, and cardiovascular conditions (4,23). To ensure early detection of these complications, it is advised that all symptomatic patients with AHP undergo abdominal and renal ultrasounds, Holter monitoring, TILT testing, ambulatory blood pressure monitoring, and echocardiography annually (4,8,13). If advanced liver fibrosis (F3 on elastography) or cirrhosis is detected, it is advisable to undergo semiannual screenings using abdominal ultrasound (40).

Asymptomatic patients should undergo annual evaluations that include a review of medical history, a physical examination, an assessment of medications, quality of life

considerations, biochemical tests (like urine ALA and PBG), a complete blood count, metabolic panel, estimated glomerular filtration rate, a hepatic function panel, and monitoring for hepatocellular carcinoma in individuals over 50 years old, which can be conducted via abdominal ultrasound and measuring plasma alpha-fetoprotein levels (8,24).

If patients are receiving prophylactic hemin therapy, ferritin and iron studies should be evaluated every three months, due to the risk of potential iron overload (4,8,30). Due to the previously mentioned side effects of givosiran, liver and renal function tests, along with total plasma homocysteine levels, should be performed monthly for the initial three months (4,8,13). After that, testing should occur every three to six months (4,8,13).

Patients receiving GnRH analogs should have annual Dual-energy X-ray absorptiometry (DEXA) and gynecological screenings (8).

Conclusion

Porphyrias are uncommon genetic and metabolic disorders caused by mutations in enzymes responsible for heme biosynthesis. This disruption results in the harmful accumulation of heme precursors, including ALA, porphobilinogen, and porphyrins, in organs like the liver, bone marrow, blood, and skin, which contributes to various symptoms. AHP is marked by sudden, severe abdominal pain, often accompanied by neuropsychiatric issues and peripheral neuropathy. Although caused by a genetic mutation, the condition exhibits low penetrance, meaning not all carriers show symptoms. Factors such as stress, fasting, or specific medications can trigger attacks, making their management crucial. Treatment includes high-glucose diets, intravenous hemin for acute attacks, and givosiran for prophylaxis of frequent attacks. Liver transplantation is still the only curative option. Although most patients remain asymptomatic between episodes, some suffer from chronic symptoms such as neuropathic pain, fatigue, neuropathy, sleep disturbances, and a decreased quality of life (41,42). Improvements in management have decreased the frequency of attacks and mortality, which is now nearly zero (43,44). Still, some patients experience residual neurological damage or chronic complications such as hypertension, kidney or liver disease, which includes an increased risk of hepatocellular carcinoma (2,4,8,43,44).

To tackle these challenges, research is investigating alternative therapies. One promising approach involves employing messenger RNA technology to restore deficient protein activity in hepatocytes using adenovirus (10,37). Other investigational therapies consist of small interfering RNA that aims to silence ALAS1 mRNA and inhibit ALAS1 protein production (38). An alternative method includes using biodegradable lipid nanoparticles to deliver porphobilinogen mRNA swiftly to the liver, ensuring uptake by hepatocytes and providing protection against porphyria attacks when given during the prodromal phase (38).

In conclusion, this review offers a valuable overview of AHP, a frequently neglected condition that necessitates increased awareness. Gaining a deeper understanding of AHP and porphyrias is essential for improving diagnosis, developing new treatments, and ultimately enhancing patient outcomes.

Figures

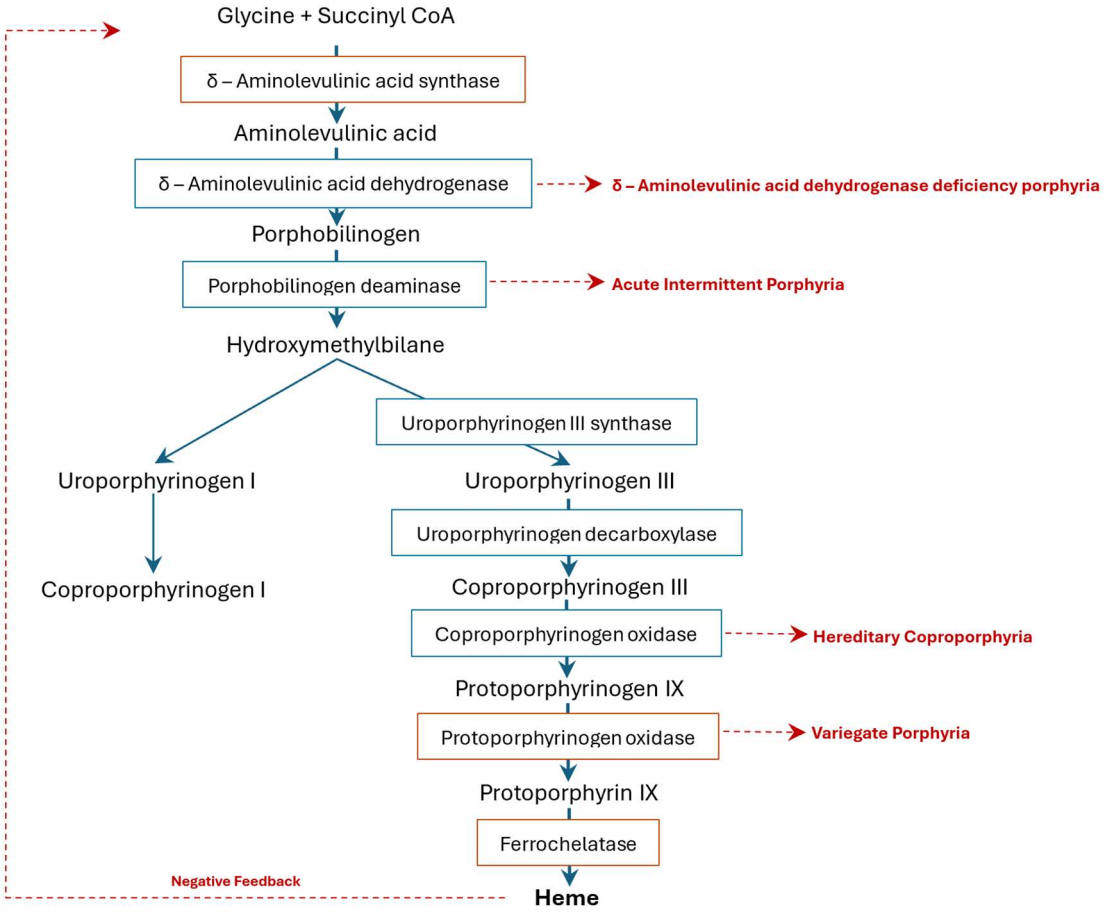

Figure 1: Heme biosynthesis and acute hepatic porphyrias, adapted from (24)

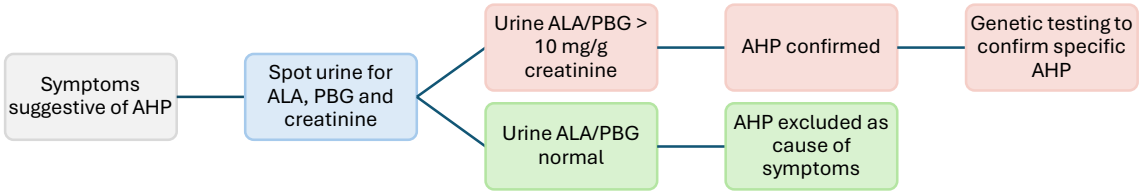

Figure 2: First-line diagnostic approach to AHP, adapted from (4)

Abbreviations: AHP, acute hepatic porphyrias; ALA, δ - aminolevulinic acid, PBG, porphobilinogen

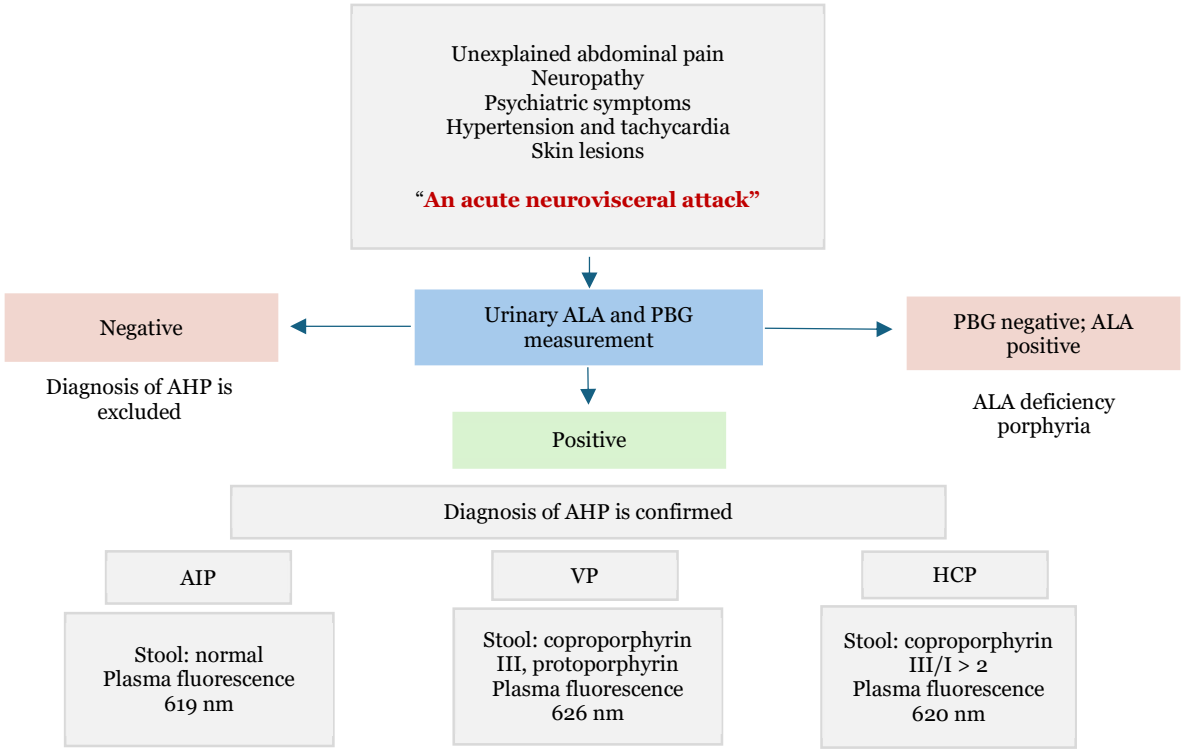

Figure 3: Diagnostic algorithm for acute hepatic porphyrias, adapted from (2)

Abbreviations: AHP, acute hepatic porphyrias; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria

Tables

Table 1: Acute hepatic porphyrias subtypes, adapted from (45–47)

Acute Porphyrias	Enzymatic Defect	Mode of Inheritance	Clinical Findings	Site of Expression	Diagnostic findings	Common mutations
Acute intermittent porphyria	PBG deaminase	Autosomal dominant	Neurologic	Liver	Urine: ALA < PBG	c.673C>T (p.R225X) c.499C>T (p.R167W) c.973C>T (p.R325X) c.76C>T (p.R26C) c.992C>T (p.A331V) c.1084delT
ALA dehydratase deficiency	ALA dehydratase	Autosomal recessive	Neurologic	Liver	Urine: ALA	c.397G>A (p.G133R) c.823G>A (p.V275M)
Hereditary coproporphyria	Coproporphyrinogen oxidase	Autosomal dominant	Neurologic, cutaneous	Liver	Urine: ALA > PBG, coproporphyrin Stool: coproporphyrin	c.520G>A (p.A174T) c.980A>G (p.H327R)
Variegate porphyria	Protoporphyrinogen oxidase	Autosomal dominant	Neurologic, cutaneous	Liver	Urine: ALA > PBG, coproporphyrin Stool: coproporphyrin, protoporphyrinogen	c.217C>G (p.L73V) c.454C>T (p.R152C) c.40G>C (p.G14R)

Abbreviations: ALA, δ-aminolevulinic acid; PBG, porphobilinogen.

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