

Acute hepatic porphyrias for the neurologist: current concepts and perspectives

Porfirias hepáticas agudas para o neurologista: conceitos atuais e perspectivas

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ABSTRACT

Background: Acute hepatic porphyrias represent an expanding group of complex inherited metabolic disorders due to inborn errors of metabolism involving heme biosynthesis. **Objective:** We aimed to review the main clinical and therapeutic aspects associated with acute hepatic porphyrias. **Methods:** The authors provided a wide non-systematic review of current concepts and recently acquired knowledge about acute hepatic porphyrias. **Results:** Acute neurovisceral attacks are the most common and life-threatening presentation of this group and are often considered the main clinical manifestation by clinicians during differential diagnosis and the start of proper diagnostic work-up for acute porphyrias. However, atypical presentations with central nervous system involvement, neuropsychiatric disturbances, and some subtypes with photosensitivity usually make the definite diagnosis difficult and late. Early therapeutic interventions are essential during emergency treatment and intercritical periods to avoid recurrent severe presentations. The availability of new disease-modifying therapeutic proposals based on small interfering RNA (siRNA)-based therapies, complementary to the classic intravenous glucose infusion and hemin-based treatments, emphasizes the importance of early diagnosis and genetic counseling of patients. **Conclusions:** This review article highlights the main biochemical, pathophysiological, clinical, and therapeutic aspects of acute hepatic porphyrias in clinical practice.







Keywords: Neuromuscular Diseases; Porphyria; Inborn Errors of Metabolism; Acute Intermittent Porphyria; Hepatic Porphyrias.

RESUMO

Introdução: As porfirias hepáticas agudas representam um grupo de doenças metabólicas hereditárias complexas em expansão, decorrentes de erros inatos do metabolismo, envolvendo a via de biossíntese do grupamento heme. **Objetivo:** realizar revisão dos principais aspectos clínicos e terapêuticos associados com as porfirias hepáticas agudas. **Métodos:** Os autores realizaram ampla revisão não-sistemática sobre conceitos atuais e conhecimentos recentemente adquiridos. **Resultados:** Ataques neuroviscerais agudos representam a apresentação clínica mais comum e de maior risco, e são comumente considerados como principal manifestação na prática clínica durante o diagnóstico diferencial e início apropriado da investigação diagnóstica para porfirias agudas. Entretanto, apresentações atípicas com envolvimento do sistema nervoso central, alterações neuropsiquiátricas e alguns subtipos com fotossensibilidade fazem com que o diagnóstico definitivo seja comumente difícil e tardio. As intervenções terapêuticas precoces são essenciais durante o tratamento emergencial e em período intercrítico evitando formas recorrentes graves. A disponibilidade de novas propostas terapêuticas modificadoras de doença baseadas em terapias com pequenas moléculas de RNA de interferência (siRNA) complementares aos clássicos tratamentos com infusão de glicose intravenosa e à base de hemina enfatiza a importância do diagnóstico precoce de tais pacientes e do aconselhamento genético. **Conclusões:** Este artigo de revisão destaca os principais aspectos bioquímicos, fisiopatológicos, clínicos e terapêuticos das porfirias hepáticas agudas na prática clínica.

Palavras-chave: Doenças Neuromusculares; Porfirias; Erros Inatos do Metabolismo; Porfíria Aguda Intermitente; Porfirias Hepáticas.

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INTRODUCTION

Porphyrias (from the Greek *Porphyros*, purple) are rare inherited metabolic disorders of the heme biosynthesis pathway, leading to the pathogenic accumulation of heme precursors (i.e., porphobilinogen and delta-aminolevulinic acid) and porphyrins. Skin and peripheral nervous system involvement arise from the toxic effects of such precursors. Porphyrias are divided according to two main categories: (i) the site of main overproduction of porphyrin precursors, including hepatic and erythropoietic porphyrias; and (ii) type of clinical presentation, including acute and chronic porphyrias^{1,2,3}.

Acute hepatic porphyrias (AHPs) represent a complex group of inborn errors of metabolism that cause acute episodic neurovisceral attacks and include four life-threatening disorders — acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and delta- or 5-aminolevulinic acid (ALA) dehydratase deficiency (or Doss porphyria) (ALADP)^{1,2,4,5,6}.

AHPs have a global and pan-ethnic distribution and affect all age groups, with higher prevalence rates among young women. AIP represents the most common form of AHP, with an estimated prevalence of 5 cases per 100,000 inhabitants in the United States (US). VP is the second (up to 1:30,000 inhabitants) and HCP the third (2:1,000,000 inhabitants in Denmark) most common form AHP. Higher prevalence rates of VP have been identified in the Afrikaner population of Dutch descent in South Africa and Finland and associated with a founder effect. ALADP is an extremely rare presentation, with little more than a dozen cases identified^{1,2,5,6}. In Brazil, epidemiological data result from information published by the Brazilian Porphyria Association (*Associação Brasileira de Porfíria* — ABRAPO) and reveal a similar prevalence of AHPs, except for the low occurrence of VP in the country⁷.

Furthermore, AHPs are associated with medical and financial burden in Europe and the US due to recurrent and extended hospitalizations, chronic and severe clinical comorbidities, and the high costs of disease-modifying therapies and medical health related to chronic complications⁸. Currently, the study of acute porphyria is crucial for the early diagnosis of debilitating disorders, proper distribution of financial resources in the health care system, and the early availability of new genetic therapies for the treatment of AHPs.

BIOCHEMISTRY AND PATHOPHYSIOLOGY

AHPs result from the deficiency of enzymes involved in the heme biosynthesis pathway, leading to the pathological accumulation of porphyrins and their intermediates. Heme is a key cofactor related to several homeostatic proteins, such as hemoglobin, myoglobin, hepatic cytochrome

P450, mitochondrial respiratory chain cytochromes, microsomal cytochrome b5, and some catalases and peroxidases. Its biosynthesis results from a multistep pathway involving eight enzymes and two cell compartments in mitochondrion and cytoplasm (Figure 1). Heme synthesis pathway occurs both in bone marrow erythroblasts (80% of total heme) and hepatocytes (20% of total heme). The rate-limiting step is represented by ALA synthase 1 (ALAS1) in the liver and ALAS2 in the erythrocyte. There is also a dependence on individual genetic factors of high susceptibility related to polymorphisms in genes associated with cytochrome P450^{2,9,10,11}.

Several pathophysiological mechanisms connected to porphobilinogen (PBG), ALA, and heme depletion in different tissues have been associated with AHPs, including complex mechanisms: (i) dysfunction of gamma-aminobutyric acid (GABA) and benzodiazepine receptors mediated by ALA; (ii) abnormal neurotransmitter and aminoacid metabolism due to ALA and PBG effects: tryptophan, glycine, acetylcholine, noradrenaline; (iii) low degree of systemic and neuronal mitochondrial oxidative capacity due to dysfunction of respiratory chain complexes; (iv) liver and neuronal dysfunction of mitochondrial cytochrome P450 related to abnormal intermediate metabolites and susceptibility gene polymorphisms; (v) persistent and prolonged ALA levels associated with chronic neurovisceral symptoms due to oxidative stress; (vi) during acute neurovisceral attacks, there is high hepatic oxidative activity of ALAS1 with secondary depletion of pyridoxal-phosphate and, thus, secondary axonal neuropathy; (vii) neurotoxic effects to axonal membrane with dysfunction of Na-K ATPase pump; (viii) protein oxidation and aggregation induced by porphyrins; (ix) nitric oxide synthase dysfunction leading to cerebral and intestinal vasospasm and abdominal pain^{2,9,11,12,13,14,15,16,17}.

CLINICAL FEATURES OF ACUTE HEPATIC PORPHYRIAS

AHPs are often misdiagnosed, and diagnostic delays of up to 15 years are sometimes observed, especially in atypical presentations and early or late-onset cases. Natural history studies have been performed, notably the EXPLORE study (NCT02240784). In this study, within a group of 112 AHP patients, 89% were female, 85% were Caucasian, the mean age at diagnosis was 39 years, and all cases emerged after puberty. Among the participants, 93% had AIP, 4% had VP, and 3% had HCP^{4,15,18}. In Brazilian patients, AIP represents 59% of cases, HCP 4%, VP 2.5%, and Doss porphyria less than 1%. Compared to the EXPLORE study, a similar profile of age at onset is identified in AHP subtypes: 40 years in AIP, 38 years in HCP, 39 years in VP, and 36 years in Doss porphyria⁷.

AHPs are typically recognized by acute neurovisceral attacks (Figure 2) with systemic and neuropsychiatric signs and symptoms (Table 1), including: (i) autonomic disturbances (i.e. gastrointestinal dysmotility, acute abdominal

pain, fever, sweating disorders, tachycardia, cardiac arrhythmia, postural hypotension, or arterial hypertension); (ii) acute neuropathic involvement (i.e., acute motor axonal neuropathy; cranial neuropathy with involvement mainly of the third, sixth, ninth, and tenth cranial nerves; neuropathic pain and acute respiratory failure with diaphragmatic paresis); (iii) metabolic disturbances (i.e., mildly abnormal liver tests and hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion); and (iv) acute neuropsychiatric disturbances or other central nervous system (CNS) involvement (i.e., acute encephalopathy, posterior reversible encephalopathy syndrome, seizures, status epilepticus, cerebral vasospasm and vasoconstriction, acute psychosis, and abnormal circadian rhythm with insomnia)^{1,2,3,4,9,13,14,15,19,20,21}.

Before a neurovisceral attack, the patient frequently experiences prodromal gastrointestinal symptoms, mainly starting with intestinal constipation and gastroparesis. Diffuse abdominal pain and abdominal distension may also occur and can be associated with urinary bladder dysfunction. According to the EXPLORE study, 69% of recurrent attacks require hospitalization, with each patient having five attacks per year with a median duration of seven days per attack (varying from 1.3 to 33.2 days). In AHPs, skin lesions in sun-exposed (photosensitive) regions are more common in the HCP and VP types and absent in AIP; they may be found from early stages of the acute attack and eventually progressing throughout the episode or only in chronic intercritical periods^{1,2,3,4,9,13,14,15,19}.

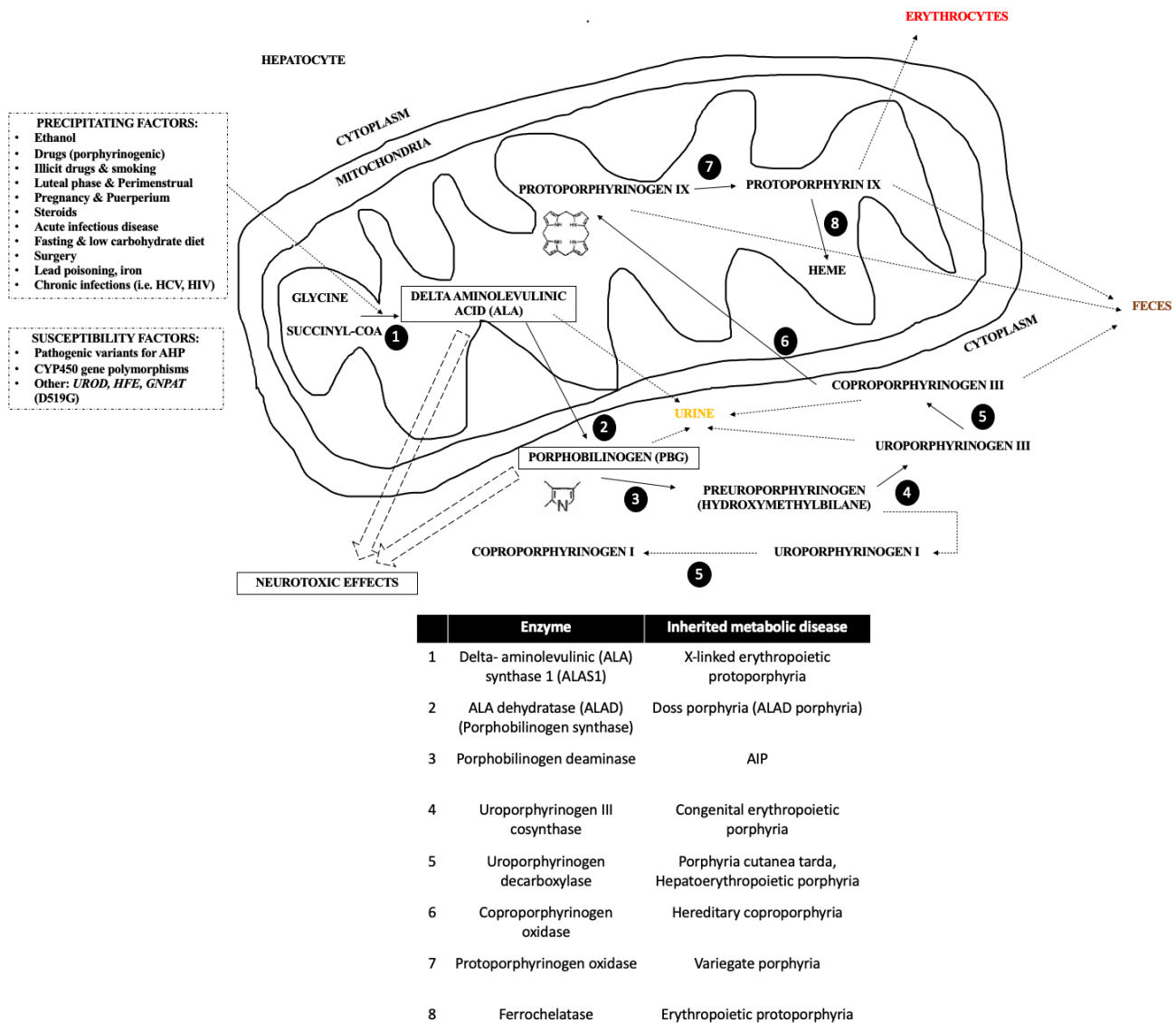
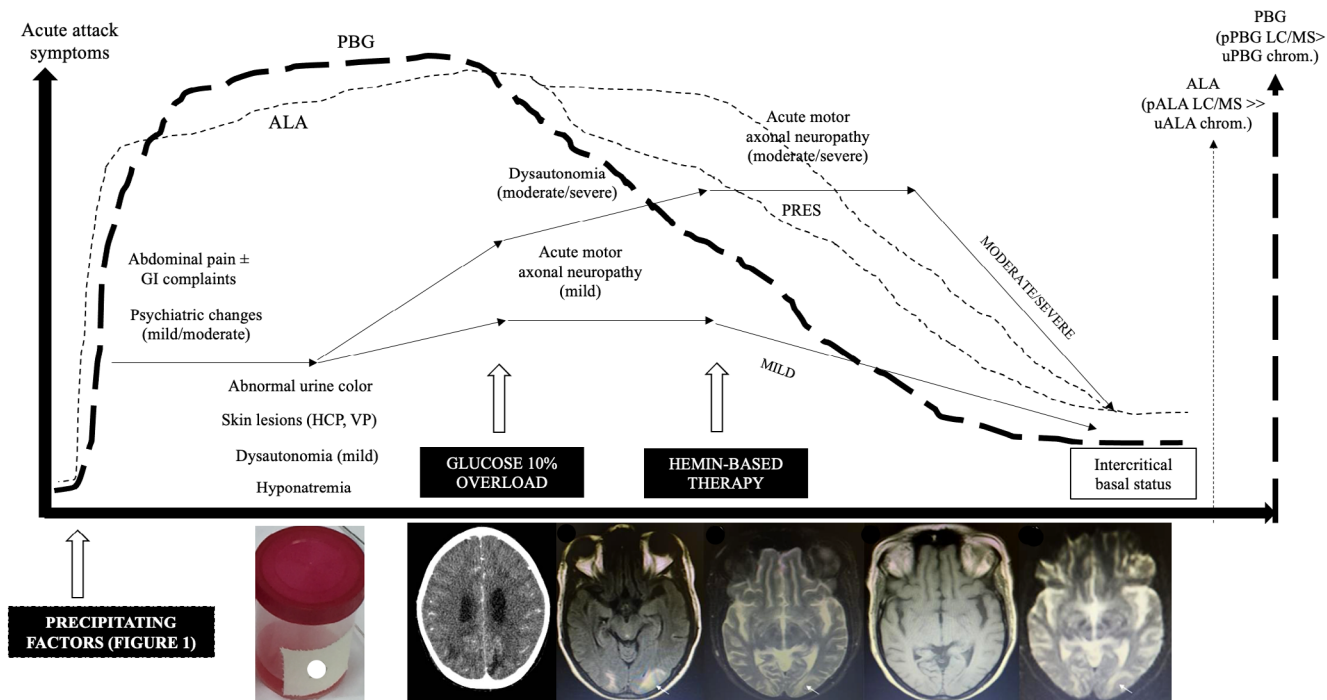


Figure 1. Metabolic heme biosynthesis pathways and pathogenesis of acute hepatic porphyrias. delta-aminolevulinic acid and porphobilinogen are involved in the most important neurotoxic effects of acute hepatic porphyrias. Precipitating and susceptibility factors are also represented and modulate the synthesis, function, or amount of delta-aminolevulinic acid synthase 1 expressed in the liver. Porphyrins and their intermediate metabolites are also represented and indicate the main excretion routes in each case (feces, urine).



ALA: delta-aminolevulinic acid; chrom.: chromatography; HCP: hereditary coproporphyria; LC/MS: liquid chromatography-mass spectrometry; PBG: porphobilinogen; PRES: posterior reversible encephalopathy syndrome; pALA: plasma ALA; pPBG: plasma PBG; VP: variegate porphyria; uALA: urinary ALA; uPBG: urinary PBG. Below: on the left side: dark-reddish urine also seen at early stages of acute attacks; on the right side: cranial computed tomography (CT) and brain magnetic resonance imaging (MRI) scans showing typical PRES neuroimaging findings in a patient with AHP during late stages of severe acute attacks.

Figure 2. Clinical progression and neurovisceral and laboratory findings during acute neurovisceral attacks in acute hepatic porphyrias, according to the time after onset and the use of glucose overload or hemin during the clinical course. The course of neurovisceral symptoms is represented by continuous black arrows in mild or moderate/severe clinical presentations. Delta-aminolevulinic acid levels are represented by thin dashed lines. Porphobilinogen levels are represented by thick dashed lines.

Table 1. Summary of the main clinical, laboratory, neurophysiological, and neuroimaging findings of each acute hepatic porphyrias.

Type of porphyria (OMIM)	Gene (locus)/Inheritance	Biochemical profile*				Skin lesions (blistering, scars...)	Neurovisceral attacks	Commentaries
		Urine	Plasma	Stool (fecal)	RBC			
AIP (#176000)	<i>HMBS</i> (11q23.3)/AD	ALA, PBG, URO I	ALA, PBG, (URO I)	Normal, COPRO I, (URO I)	Low HMBS enzyme	Absent	+++ motor axonal, dysautonomia	High risk for HCC; most severe neurological symptoms; atypical presentation in AR cases
HCP (#121300)	<i>CPOX</i> (3q11.2)/AD	ALA, PBG, COPRO III, URO I	COPRO	COPRO III ++, PROTO, URO	Normal	+ /+++ skin ≥ neuropathy	+ /+++ motor axonal > dysautonomia	Plasma fluorescence emission peak wavelength at 620 nm; high risk for HCC; atypical presentation in AR cases
VP (#176200)	<i>PPOX</i> (1q23.3)/AD	ALA, PBG, COPRO III, URO I	Porphyrin conjugate, PROTO, COPRO III	PROTO ++, COPRO III, (URO)	Normal	+ /+++ skin ≥ neuropathy	+ /+++ motor axonal > dysautonomia	Plasma fluorescence emission peak wavelength at 624-628 nm; high risk for HCC; atypical presentation in AR cases
ALA dehydratase deficiency (#612740)	<i>ALAD</i> (9q32)/AR	ALA, (COPRO III)	ALA	Normal	Zn-PROTO; low ALAD activity	Absent	+	Very rare; most cases in men; some cases associated with hemolytic anemia

AD: autosomal dominant; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: delta-aminolevulinic acid; ALAD: delta-aminolevulinic dehydratase gene; AR: autosomal recessive; COPRO: coproporphyrin; CPOX: coproporphyrinogen oxidase gene; HCC: hepatocellular carcinoma; HCP: hereditary coproporphyria; HMBS: hydroxymethylbilane synthase gene; PBG: porphobilinogen; PPOX: protoporphyrinogen oxidase gene; PROTO: protoporphyrin; RBC: red blood cell (erythrocyte); URO: uroporphyrin; VP: variegate porphyria; Zn: Zinc; +: mild; ++: moderate; +++: severe. *During remission, intercritical periods, or in asymptomatic carriers, values and metabolic profiles may differ from the biochemical profile seen in symptomatic patients during acute attacks. Normal urinary, fecal, and blood levels of precursors and porphyrins may also be different among genetically distinct populations.

Other clinical presentations include acute dysautonomia or acute flaccid paralysis in the intensive care unit as a differential diagnosis in patients with suspected critical illness polyneuropathy. Atypical presentations include pure dysautonomia, CNS involvement, and late-onset pure neuropsychiatric disturbances. Other psychiatric contexts may also be found, including catatonia, delusions, mood and behavioral changes, visual and auditory hallucinations, paranoid psychosis, or late-onset personality disorders^{1,2,3,4,9,13,14,15,19,20,21}.

In the EXPLORE study, besides neuropsychiatric disorders (up to 30% of cases), long-term disease complications include chronic kidney disease (up to 8% of cases), hepatocellular carcinoma²², and chronic systemic arterial hypertension (up to 23% of cases)¹⁸. They occur more often in patients with a recurrent disease course. Iron overload with liver fibrosis and cirrhosis is also observed after chronic treatment with heme therapy²³. Moreover, AHPs cause severe impairment of quality of life: 46% of patients have chronic daily symptoms, such as gastrointestinal dysmotility in 30% of cases, chronic pain in 20%, and chronic fatigue and sleep disorders in 15%¹⁸.

Acute intermittent porphyria

AIP (Online Mendelian Inheritance in Man — OMIM #176000), formerly known as Swedish type porphyria, is an autosomal dominant inherited metabolic disorder resulting from heterozygous pathogenic variants in the *HMBS* gene (11q23.3), encoding cytoplasmic hydroxymethylbilane synthase (porphobilinogen deaminase), leading to the abnormal conversion of porphobilinogen into hydroxymethylbilane. AIP is the most common form of AHP. Despite its global and pan-ethnic distribution, it has been widely described in northern Sweden with a founder effect with the pathogenic variant c.593G>A (p.Trp198Ter). Other familial aggregations were described in Murcia (Spain) and in the UK^{3,15,24,25}.

AIP presents with the typical clinical features observed in most AHPs. Most cases are associated with a classic acute neurovisceral presentation without skin lesions. However, only 10 to 20% of AIP gene mutation carriers become symptomatic during their lifetime. Furthermore, the classic form (95% of cases) results from erythroid isoform deficiency, while only 5% of cases may be caused by a variant with ubiquitous nonerythroid isoform deficiency, both with similar clinical features^{3,15,24,25}. Peripheral, autonomic, and CNS involvement are common in AIP. CNS involvement is observed in different contexts, including: (i) unexplained cerebral vasospasm with ischemic brain areas²⁶; (ii) posterior reversible encephalopathy syndrome (PRES); (iii) hemorrhagic stroke and cerebral vasospasm; (iv) reversible cerebral vasoconstriction syndrome; (v) severe hyponatremia complicating central pontine and extrapontine myelinolysis^{20,26,27}. Regarding peripheral nervous system involvement, acute neuropathic pain due to small-fiber neuropathy is classically recognized, sometimes as a presenting feature, and can precede motor and autonomic involvement from

several days to weeks²⁸. During acute attacks, most patients progress to acute axonal polyneuropathy and asymmetrical motor involvement, starting in proximal regions of the upper limbs. Diaphragmatic and cranial nerve involvement may occur²⁹. AIP is currently considered a key differential diagnosis of recurrent or refractory Guillain-Barré syndrome (GBS). Acute episodes in AIP tend to present with severe bulbar involvement and early and more prominent acute respiratory failure than in other AHPs. Rhabdomyolysis and cortical blindness have also been described in AIP^{1,22}. Only 5% of patients have recurrent acute attacks, defined as four or more attacks per year, more commonly found in women and precipitated in the perimenstrual period, pregnancy, puerperium, and by porphyrinogenic drugs^{28,30}.

Regarding women of childbearing age with AIP, pregnancy means a high-risk period for maternal and fetal health. It represents a high risk of intrauterine growth retardation in fetuses, low birth weight in newborns, premature delivery, and higher rates of perinatal mortality. Women with AIP are at high risk during pregnancy or after delivery for pre-eclampsia, PRES, neuropsychiatric disturbances, and other CNS vascular complications, including cerebral vasospasm and ischemic stroke³¹.

Long-term follow-up reveals three possible clinical outcomes: (i) asymptomatic latent AIP; (ii) active phase (1–2 years) with acute attacks and long-lasting clinical remission or few sporadic minor attacks; (iii) recurrent attacks since the first episodes and no long-term biochemical remission, requiring chronic administration of heme³². However, chronic systemic complications may arise in AIP, similar to other AHPs, with high risk for early-onset chronic kidney disease secondary to tubulointerstitial nephropathy, hepatocellular carcinoma, and porphyria-induced hypertension^{1,22}.

Biochemical evaluation gives important clues about AIP suspicion during acute episodes; nevertheless, metabolic work-up during asymptomatic or intercritical periods is commonly unremarkable. Urinary samples are critical during AIP evaluation, with markedly elevated urinary porphyrin levels, mostly with high uroporphyrin and PBG levels. Qualitative tests (Watson-Schwartz or Hoesch tests) are often used to characterize positive (elevated amount of PBG) or negative results based on spot urine samples with low diagnostic sensitivity and specificity. Measuring PBG in a 24-hour specimen by quantitative methods offers better results. Urinary PBG levels in AIP remain high between acute attacks for longer periods than other AHPs. In addition, urinary PBG is almost always normal in asymptomatic individuals with genetically proven AIP. Fecal porphyrin levels are normal in AIP or, in rare cases, slightly increased. During acute episodes, plasma porphyrin levels are normal or slightly increased and do not correlate with clinical severity. Enzyme profile in liver and erythrocytes and gene mutations in AIP present distinct patterns: (i) 10% with normal enzyme activity in erythrocytes, but defective expression in other tissues; (ii) about 10%

have enzyme reduction to a minimal extension in erythrocytes (indeterminate zone); (iii) all other cases have enzyme reduction in liver, erythrocytes, and other tissues. Almost 96% of cases present pathogenic variants in the *HMBS* gene, detected by sequence analysis^{3,9,33}.

Autosomal recessive presentations are associated with distinct phenotypes and typical biochemical findings observed in AIP. Autosomal recessive childhood-onset cases result from compound heterozygous gene mutations in the *HMBS* gene with complex clinical findings, including: (i) porencephaly, neuropsychomotor developmental delay, and excessive urinary ALA, PBG, and uroporphyrin³⁴; (ii) childhood-onset mild chronic anemia, hepatosplenomegaly, mild intellectual disability, yellow-brown teeth, dark urine with highly elevated levels of urinary uroporphyrin, ALA, PBG, and raised urinary levels of hepta-, penta-, hexa- and coproporphyrins³⁵; and (iii) severe encephalopathy due to R167W homozygous pathogenic variant, with early childhood lethality, severe psychomotor delay, axonal neuropathy, diffuse leukoencephalopathy, and high urinary levels of porphyrins³⁶. Bi-allelic *HMBS* missense compound heterozygous pathogenic variants have also been associated with complex neurological phenotypes, including childhood-onset progressive spastic ataxia, neuropathy, optic atrophy, nystagmus, vertical gaze palsy, and diffuse leukoencephalopathy, besides moderate rise in urinary PBG and plasma ALA^{37,38}.

Hereditary coproporphria

HCP (OMIM #121300) is an autosomal dominant inherited metabolic disorder caused by heterozygous pathogenic variants in the *CPOX* gene (3q11.2), which codes for mitochondrial coproporphyrinogen III oxidase (CPOX), leading to deficiency in the conversion of coproporphyrinogen III into protoporphyrinogen IX. Symptomatic patients have markedly decreased CPOX activity to less than 5% in lymphocytes. Typical acute neurovisceral attacks in HCP usually start after the third decade of life. Most individuals present with lower back pain and recurrent abdominal pain, besides skin photosensitivity in 15% of cases. Skin involvement is observed in sun-exposed areas with bullae, hypertrichosis, and hyperpigmented scars. Pure acute neurovisceral attacks are seen in 72% of cases, while 7% present with pure dermatological signs, and only 21% have both dermatological and neurovisceral symptoms. CNS involvement is also reported, including PRES episodes²⁰, cerebral vasospasm with ischemic stroke, refractory epilepsy partialis continua, and status epilepticus. Screening for chronic complications is mandatory and involves evaluation of liver fibrosis and annual screening for hepatocellular carcinoma with serum alpha-fetoprotein and abdominal imaging studies in patients older than 50 years^{14,15,17}.

Biochemical evaluation indicates a suggestive metabolic profile in most cases: (i) elevated fecal porphyrin levels, mainly with fecal coproporphyrin isomer III (without

significant fecal protoporphyrin elevation); (ii) markedly elevated urinary porphyrin levels, mostly coproporphyrin III/I isomer ratio >1.5 with mildly to moderately elevated PBG levels; (iii) normal plasma porphyrin levels are common, despite a slight increase in some patients with skin involvement; (iv) plasma fluorescence emission spectroscopy with a peak wavelength at 615–620 nm. Gene sequencing analysis is the gold-standard definitive method for diagnosis and identifies pathogenic variants in more than 95% of patients with HCP^{3,9,15}.

Harderoporphyria is an autosomal recessive erythropoietic variant of HCP caused by compound heterozygous or homozygous pathogenic variants in the *CPOX* gene, affecting the conversion of harderoporphyrinogen into protoporphyrinogen IX. Its clinical presentation is distinct from that of classic HCP and includes neonatal hemolytic anemia, neonatal jaundice, and mild chronic anemia during childhood and adulthood. Hepatosplenomegaly and dark-reddish urine may also be observed. Blistering lesions with photosensitivity occur in 20% of cases. Acute neurovisceral attacks are rare during adulthood. Elevated liver enzymes and mild metabolic acidosis can be detected at early stages. Massive excretion of harderoporphyrin in feces is a hallmark of the disorder³⁹.

Variegate porphyria

VP (OMIM #176200), formerly called South African type porphyria, is an autosomal dominant inherited metabolic disorder resulting from heterozygous pathogenic variants in the *PPOX* gene (1q23.3), leading to protoporphyrinogen oxidase (PPOX) deficiency and reduced conversion of protoporphyrinogen IX into protoporphyrin IX. VP has a regional founder effect in South Africa among the Afrikaner population of Dutch descent, showing the pathogenic variant c.175C>T(p.Arg59Trp). Almost 59% of cases present with pure dermatological signs, 20% with pure acute neurovisceral attacks, and only 21% with both skin and neurological involvement. Postinflammatory facial and limb hyperpigmentation, hypopigmented skin patches, hypertrichosis, skin fragility, chronic blistering lesions, subepidermal vesicles, and bullae are common dermatological complaints¹⁷. Motor axonal neuropathy and dysautonomia during acute attacks are similar to other AHPs. Acute encephalopathy, PRES, and behavioral changes are rare neurological presentations. The risk for chronic kidney disease and hepatocellular carcinoma is also high, making routine diagnostic screening necessary^{3,15,20,40}.

Metabolic profile may give important diagnostic clues. Increase in urinary ALA, PBG (rarely with normal PBG levels), and porphyrins during acute attacks is common, and, in most cases, urinary porphyrins (coproporphyrin) remain elevated even when urinary PBG levels return to normal. Urinary PBG and ALA levels become normal earlier in VP than in AIP after acute attacks. During intercritical

periods or in asymptomatic patients, the urinary metabolic profile may be almost normal. Elevated fecal levels of protoporphyrin and coproporphyrin isomer III may be observed during or after acute attacks. Markedly elevated plasma porphyrin levels are common during acute attacks and present a distinctive fluorescence peak wavelength at 626 nm (624–627) on fluorescence scanning of diluted plasma at neutral pH^{3,9,14,15,30}.

Homozygous variants with atypical presentations have been associated with complex neurological and systemic contexts due to severe PPOX deficiency, including early childhood- or neonatal-onset photosensitization, bullous lesions, skin fragility, keloid scarring, short stature, skeletal abnormalities, intellectual disability, epileptic encephalopathy, and sometimes IgA nephropathy. Acute neurovisceral attacks are not observed in such cases. The analysis of PPOX enzyme activity in lymphocytes reveals very low levels, and the concentration of protoporphyrins in erythrocytes is high^{41,42}.

Doss porphyria (5-aminolevulinic acid dehydratase deficiency)

Doss porphyria (OMIM #612740) is an extremely rare autosomal recessive inherited metabolic disorder caused by compound heterozygous or homozygous pathogenic variants in the *ALAD* (9q32) gene, coding the cytoplasmic ALA dehydratase (ALAD, porphobilinogen synthase), resulting in the abnormal conversion of ALA into porphobilinogen. Cases have been mainly described in male patients from Sweden and Germany without skin lesions; however, two Brazilian women have also been identified. Most cases have a childhood or juvenile onset. Its clinical course is similar to but more severe than that of other AHPs due to almost complete enzymatic deficiency (less than 3% of normal enzyme activity). Biochemical work-up shows ALA increases in plasma and urine, elevated urinary coproporphyrin, and erythrocyte protoporphyrin^{7,15,43,44}.

DIAGNOSTIC APPROACH TO HEPATIC PORPHYRIAS

AHPs must be included in the differential diagnosis of cases with motor-predominant (or pure) axonal neuropathy associated with neuropsychiatric manifestations and gastrointestinal or abdominal involvement (neurovisceral involvement). Any patient with this clinical picture should be carefully considered for AHP diagnostic work-up (Table 2)^{3,25,33,45}. Several different diagnostic methods are currently available for AHP evaluation. Specific genetic testing using Sanger sequencing or next-generation sequencing (NGS) strategies (including *HMBS*, *CPOX*, and *PPOX* genes) or the analysis of specific familial pathogenic variants are gold-standard diagnostic methods for AHPs. DNA testing is usually requested after initial biochemical screening tests (urinary, stool, and plasma porphyrins and porphyrin precursors or specific enzyme assays) (Figure 3). If genetic testing is not available and patients are in the intercritical period, full biochemical testing is indicated, including fecal porphyrins, plasma porphyrins, and urinary ALA, PBG, and porphyrins. Since biochemical profile results can be frequently inconclusive, urinary PBG and ALA (24-hour sample), plasma porphyrins, and fecal porphyrins should be ideally evaluated at the same time. If urinary PBG is normal, total porphyrins and ALA from the same sample should be evaluated in highly suspicious cases. Normal PBG levels do not rule out AHPs, such as ALA dehydratase deficiency. Enzyme activity assays in erythrocytes (i.e., PBG deaminase) or lymphocytes can also be used during diagnostic work-up. Qualitative testing (i.e., calorimetric methods like Watson-Schwartz and Hoesch tests for PBG) must be confirmed by quantitative techniques or genetic testing. Currently, plasma PBG evaluation by liquid chromatography-mass spectrometry (LC-MS) represents the most sensitive biomarker available to monitor clinical and therapeutic responses after acute episodes, if compared to urinary PBG and ALA by ion-exchange chromatography^{3,4,6,25,33,45}.

Table 2. Clinical (neurological and systemic), laboratory, neurophysiological, and neuroimaging findings of high suspicion for a possible acute hepatic porphyrias.

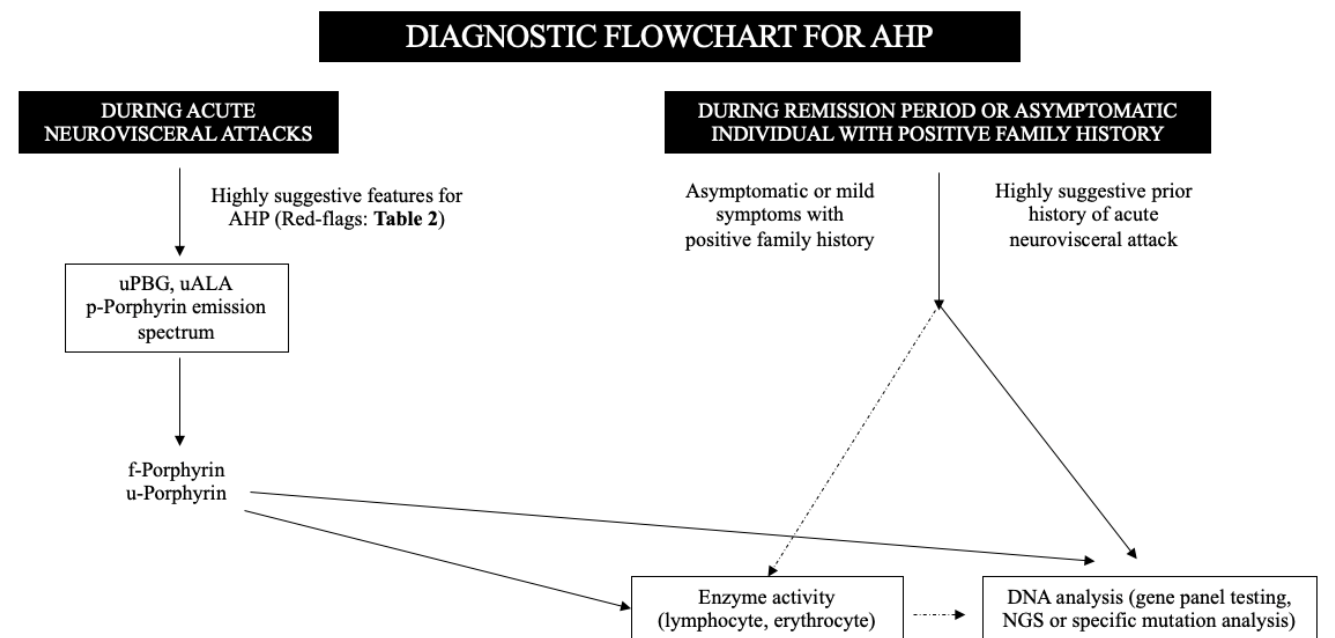
Clinical, laboratory, neurophysiological, and neuroimaging findings indicating possible AHP
1. Acute or subacute-onset flaccid paralysis (proximal and upper limb-dominant weakness) in the ED/ICU, especially in case of: (i) prior chronic or subacute history of behavioral or neuropsychiatric changes (i.e., mood or psychotic changes); (ii) moderate to severe hyponatremia; (iii) severe dysautonomic changes (i.e., usually pandysautonomia in the ICU); (iv) severe abdominal pain with/without dark urine; (v) blistering skin changes involving hands or face; (vi) positive family history of AHP cases or possible diagnosis; (vii) normal CSF analysis; (viii) positive history of exposure to potentially porphyrinogenic precipitants (i.e., drugs, chronic lead poisoning, premenstrual period).
2. Recurrent episodes of GBS, especially if an axonal pattern of involvement is present (with/without skin lesions), normal CSF analysis or if associated with CNS complications (i.e., PRES, cerebral vasospasm).
3. Late-onset subacute or acute neuropsychiatric disturbances (i.e., psychosis) or refractory status epilepticus (i.e., acute encephalopathy) in the context of hyponatremia, catamenial (mainly premenstrual) or potential history of drug precipitated (evoked) episode
4. Recurrent episodes of abdominal pain without peritoneal signs (i.e., commonly with a prior history of acute abdomen with surgical procedures) but associated with: (i) dark-reddish or purple (port-wine) urine; (ii) recurrent hyponatremia; (iii) dysautonomic involvement; (iv) skin lesions in photosensitive areas (i.e., HCP, VP); (v) acute or chronic painful small-fiber neuropathy.
5. Painful small-fiber axonal neuropathy with associated gastrointestinal complaints and neuropsychiatric disturbances.

AHP: acute hepatic porphyria; CNS: central nervous system; CSF: cerebrospinal fluid; ED: emergency department; GBS: Guillain-Barré syndrome; HCP: hereditary coproporphyrin; ICU: intensive care unit; PRES: posterior reversible encephalopathy syndrome; VP: variegate porphyria.

DIFFERENTIAL DIAGNOSIS

The group of clinical conditions that make a differential diagnosis with AHPs is broad and can be best evaluated based on the main clinical and neuromuscular signs involved (Table 3). Clues for considering AHPs include: (i) acute flaccid paralysis mainly with acute motor axonal involvement; (ii) severe dysautonomia; (iii) hyponatremia;

(iv) CNS involvement, including PRES, neuropsychiatric disturbances, and acute epileptic encephalopathy; and (v) dark-reddish urine. Pure severe dysautonomic presentations with associated complex cardiac arrhythmia must also be considered. Cases without skin involvement must refer to AIP and rarely to Doss porphyria, but VP and HCP presentations limited to neurological involvement must also be considered^{2,4}.



AHP: acute hepatic porphyrias; ALA: delta-aminolevulinic acid; f: fecal; NGS: next-generation sequencing; p: plasma; PBG: porphobilinogen; uALA: urinary ALA; uPBG: urinary PBG.

Figure 3. Diagnostic flowchart for the clinical, metabolic, and genetic evaluation of suspected acute hepatic porphyrias.

Table 3. Main differential diagnosis of acute hepatic porphyrias during acute neurovisceral attacks and chronic presentation.

Differential diagnosis of AHPs during acute neurovisceral attacks and chronic presentation	
1. Acute flaccid paralysis	GBS and variants; acute viral poliomyelitis (and polio-like virus); botulism; myasthenic crisis; periodic paralysis; HIV seroconversion; rhabdomyolysis; acute transverse myelitis; tick-paralysis; neuroparalytic snake envenomation.
2. Acute dysautonomia	GBS and variants; paraneoplastic disorders; idiopathic autoimmune postganglionic dysautonomia; systemic autoimmune disorders; toxic neuropathies.
3. Painful small-fiber neuropathy	Fabry disease; diabetes; hereditary <i>TTR</i> -related amyloidosis; toxic neuropathies; paraproteinemia; primary amyloidosis; paraneoplastic neuropathy; complex regional pain syndrome; vasculitis.
4. Neuropsychiatric disturbances	Primary psychiatric disorders; autoimmune encephalitis; brain tumor; other inherited neurometabolic disorders.
5. PRES	Hypertensive encephalopathy; neuroimmune disorders of the CNS; systemic inflammatory conditions; drug adverse/toxic event.
6. Dark-reddish urine	Drug-induced urine color; choloria; renal lithiasis; urinary tract infection; purple urine bag syndrome (urinary tract infection by <i>Providencia sp.</i> , <i>Klebsiella sp.</i> , <i>Escherichia coli</i> , <i>Enterococcus sp.</i> , <i>Pseudomonas sp.</i>); macroscopic hematuria due to urinary tract neoplasia.
7. Abdominal pain with/without constipation	Deeply infiltrating endometriosis; pelvic congestion syndrome; chronic functional constipation; acute abdomen; inflammatory bowel disease; chronic lead poisoning.
8. Skin lesions	Cutaneous porphyrias; congenital epidermolysis bullosa; autoimmune bullous disorders; erythema multiforme; toxic epidermal necrolysis; paraneoplastic pemphigus; bullous pemphigoid; systemic vasculitis; staphylococcal scalded skin syndrome.

Legends: AHPs: acute hepatic porphyrias; CNS: central nervous system; GBS: Guillain-Barré syndrome; HIV: human immunodeficiency virus; PRES: posterior reversible encephalopathy syndrome; *TTR*: transthyretin.

THERAPEUTIC APPROACHES

The management of acute and chronic complications involve several different approaches, including: (i) treatment of acute neurovisceral attacks; (ii) treatment during the intercritical period or after acute attacks; and (iii) prevention of recurrent attacks and chronic long-term complications^{2,3,4,6,46,47}. During an acute AHP presentation, evaluating its severity with a specific score is essential and can aid clinicians to predict overall outcomes and prognosis, including five different domain:

- (i) assessment of muscle strength by the Medical Research Council (MRC) sum-score (0: MRC 55–60; 1: MRC 45–54; 2: MRC 35–44; 3: MRC 25–34; 4: MRC 15–24; 5: MRC 5–14; 6: MRC 0–4);
- (ii) mechanical ventilation (0: no; <2 weeks: 2; 2–4 weeks: 4; >4 weeks: 6);
- (iii) bulbar involvement with dysarthria, dysphonia, or dysphagia (0: absent; 6: present);
- (iv) consciousness (0: normal; 2: lethargy; 4: stupor; 6: coma);
- (v) hyponatremia (0: >132 mmol/L; 3: >120 mmol/L; 6: <120 mmol/L)⁴⁸.

According to the total score, during the nadir of an acute attack, clinical manifestations are classified as:

- (i) score 0: mild episode, only mild dysautonomia;
- (ii) score 1–4: moderate episode, with dysautonomia and hyponatremia, lethargy, seizures, or flaccid paralysis, without mechanical ventilation;
- (iii) score 5–25: severe episode, with severe dysautonomia and flaccid paralysis, bulbar palsy, mechanical ventilation, severe hyponatremia, and stupor/coma;
- (iv) score 26–30: critical episode, with severe dysautonomia, severe motor involvement, coma, long-lasting mechanical ventilation, and high risk of death⁴⁸.

The treatment of acute attacks involves different therapeutic measures, such as hemin-based therapies; infusion of high doses of glucose; screening, identification, and treatment of triggering factors; review of harmful drugs; supportive treatment (fluid and electrolyte therapy and dietary support); and education about AHPs and their red-flag signs⁴⁷. During acute attacks, the first steps are:

- (i) detailed evaluation of medical prescription (searching for porphyrinogenic drugs) (Table 4);
- (ii) general supportive treatment (i.e., correction of electrolyte disturbances, mainly hyponatremia and hypomagnesemia, stabilization of dysautonomia);
- (iii) removal of precipitating factors (i.e., alcoholic beverages, prolonged fasting, restrictive low-carbohydrate diets, Atkins diet, smoking, anesthetic agents, strenuous physical exercise, emotional stress, pregnancy, puerperium);
- (iv) treatment of seizures and status epilepticus with safe drugs (including propofol, benzodiazepines, gabapentin, and vigabatrin); and

- (v) start of glucose overload therapy. Refractory seizures in acute episodes, progressive acute motor neuropathy, severe hyponatremia, and early autonomic disturbances represent red-flags, indicating a life-threatening episode and the need for management in an intensive care unit. Important variations can be found in safe drug list criteria among specialized centers. In this context, we present data from the Drug Database for Acute Porphyria, which is annually updated by the UK Porphyria Medicines Information Service (UKPMIS), the Cardiff Porphyria Service, and the National Acute Porphyria Service (NAPS) (Table 4)^{6,22}.

Intravenous dextrose (or glucose) infusion and high oral carbohydrate intake are key therapeutic approaches during mild to moderate acute episodes. A glucose loading of 300–500 g daily by intravenous infusion for 2–3 days is the most common therapy. Hyperglycemia promotes downregulation of ALAS1 expression by intracellular pathways related to peroxisome proliferator-activated receptor-gamma coactivator 1 α (PGC-1 α)^{4,6,46}. Hemodialysis and hemoperfusion are also alternative therapies in moderate to severe acute attacks in patients without access to hemin-based therapies (further discussed) and without marked response to glucose infusion⁴⁹.

Hemin is an oxidized form of human iron protoporphyrin IX from blood donors. Hemin-based therapies are well-known options for the treatment of moderate to severe neurovisceral attacks, refractory attacks to high carbohydrate overload, and recurrent attacks as prophylactic therapy. After intravenous infusion, heme circulates as heme-albumin and is taken by hepatocytes, promoting downregulation of hepatic ALAS1 biosynthesis. Several protocols are used for intravenous infusion of hemin as heme arginate (Normosang[®], from Orphan Drug Europe) or hema-tin (Panhematin[®], from Recordati Rare Diseases Inc and Ovation Pharmaceuticals). Panhematin[®], a product of the reaction of hemin with sodium carbonate, is a lyophilized preparation of hydroxyheme (350 mg hemin per vial) used with the standard dosage of 3–4 mg per kg, once daily, for 4–5 days. Weekly or biweekly infusions are used for chronic prophylactic purposes. Clinical evidence of Panhematin use has emerged from five open-label multicenter compassionate-use studies, including 229 AHP patients, most of them with AIP⁵⁰. Panhematin reduces motor weakness and acute pain (especially abdominal pain) by 85.5% and completely improves biochemical markers during acute attacks. It is the only US Food and Drug Administration (FDA)-approved therapy during acute attacks in women with recurrent attacks related to the menstrual cycle and refractory attacks after carbohydrate therapy. Adverse events can occur after reconstitution with sterile water with mild transient anticoagulant effects and local phlebitis. Acute tubular necrosis has been associated with a

Table 4. Current list of some of the drugs that are considered safe for acute hepatic porphyria patients*. In the context of drugs with uncertain or doubtful safety profiles, the recommendation is to choose alternate safe drugs.

Safe drugs and therapeutic options for the treatment of acute hepatic porphyria patients**	
Anesthetics	General anesthesia: Desflurane, Isoflurane, Propofol, Sevoflurane; Local use: Bupivacaine, Ethyl chloride, Prilocaine, Procaine, Tetracaine; Neuromuscular blockers: Pancuronium, Succinylcholine, Vecuronium.
Antineoplastic agents	Radioactive Iodine (I-131), Actinomycin D, Adriamycin, Amifostine, Asparaginase, Bleomycin, Carboplatin, Cisplatin, Cytarabine, Doxorubicin, Fludarabine, Thioguanine.
Antimicrobial agents	Aminoglycosides (Amikacin, Gentamicin, Streptomycin, Tobramycin); Antifungal agents (Amphotericin B, Caspofungin, Flucytosine, Nystatin); Antimalarials (Chloroquine, Atovaquone, Mefloquine, Primaquine, Proguanil, Pyrimethamine); Antimycobacterial agents (Ethambutol); Antiretroviral drugs (Abacavir, Zalcitabine); Antivirals (Acyclovir, Adefovir, Famciclovir, Foscarnet, Ganciclovir, Ribavirin, Valacyclovir, Valganciclovir, Zanamivir); Carbapenems (Doripenem, Imipenem, Meropenem); Cephalosporins (Cefaclor, Cefazolin, Cefepime, Cefotetan, Cefoxitin, Cefpodoxime, Ceftazidime, Ceftriaxone, Cefuroxime, Cephalexin); Fluoroquinolones (Ciprofloxacin); Penicillins (Amoxicillin, Amoxicillin/Clavulanate, Ampicillin, Penicillin, Piperacillin, Ticarcillin); Vancomycin.
Cardiovascular therapies	Antihypertensive drugs (Benazepril, Captopril, Enalapril, Lisinopril, Ramipril, Trandolapril; Candesartan, Losartan, Olmesartan, Valsartan, Eprosartan, Irbesartan, Telmisartan), Lipid-lowering drugs (Cholestyramine, Clofibrate, Colestipol, Ezetimibe, Rosuvastatin), Beta-blockers (Atenolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nadolol, Pindolol, Propranolol, Sotalol, Timolol), Diuretics (Acetazolamide, Amiloride, Bumetanide, Furosemide); Antiarrhythmic drugs (Adenosine, Digoxin, Flecainide, Procainamide), Isosorbide dinitrate, Diazoxide, Vasopressors (Dobutamine, Dopamine, Ephedrine).
Hematologic treatment	Anticoagulants (Unfractionated Heparin, Abciximab, Dabigatran, Dalteparin, Dipyridamole, Enoxaparin, Eptifibatide, Lepirudin, Protamine, Warfarin), Hemostatic agents (Aminocaproic acid, Aprotinin); Thrombolytic enzymes (Alteplase, Streptokinase, Tenecteplase); Tranexamic acid, Clopidogrel, Hydroxyethyl starch for plasma replacement, Filgrastim, Epoetin alfa, Cyanocobalamin.
Hormone therapy	Corticosteroids (Betamethasone, Cortisone, Fludrocortisone, Hydrocortisone, Prednisone, Triamcinolone), Conjugated estrogens, LHRH/GnRH agonists (Goserelin, Nafarelin), Ovulation stimulants (Clomid), Pituitary hormones (vasopressin/desmopressin, ergonovine, menotropin, methylergonovine, oxytocin, urofollitropin), chorionic gonadotropin, thyroid therapies (levothyroxine, liothyronine, propylthiouracil), octreotide, calcitonin.
Immunotherapy and vaccines	Abatacept, Adalimumab, Alemtuzumab, Anakinra, Belimumab, Certolizumab, Denosumab, Etanercept, Golimumab, Infliximab, Natalizumab, Rituximab; Interferon Alfa-2A or -2B, Interferon Gamma-1B; Antimicrobial vaccines: influenza, hepatitis B and A, Measles, Mumps & Rubella, Pneumococcal, Polio, Varicella; toxoids (Diphtheria, Tetanus, acellular Pertussis); Antivenoms**; Azathioprine**.
Gastrointestinal drugs	H2 Antagonists (Cimetidine, Ranitidine), Antiemetics (Meclizine, Ondansetron), Bisacodyl, Esomeprazole, Omeprazole, Pantoprazole, Hyoscyamine, Scopolamine, Atropine, Loperamide, Senna.
Neuropsychiatric drugs	Antidepressants (Amitriptyline, Citalopram, Fluoxetine, Mirtazapine), Antiepileptic drugs (Gabapentin, Levetiracetam, Pregabalin, Vigabatrin, Zonisamide), Antimyasthenic agents (Amibenonium, Edrophonium, Neostigmine, Pyridostigmine), Antiparkinsonian drugs (Amantadine, Entacapone, Levodopa, Levodopa/carbidopa, Pramipexole), Benzodiazepines (Clobazam, Lorazepam, Oxazepam, Temazepam, Triazolam), Hypnotics (Chloral hydrate, Zolpidem), Neuroleptics and others (Chlorpromazine, Clozapine, Fluphenazine, Haloperidol, Lithium, Perphenazine, Prochlorperazine, Thioridazine), Tropicium, Baclofen.
Pain therapy	Nonsteroidal anti-inflammatory drugs (Acetaminophen, Aspirin, Ibuprofen, Indomethacin, Ketoprofen, Naproxen, Sulindac), Narcotics (Alfentanil, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone); Antiepileptic drugs.
Respiratory agents	Acetylcysteine, Albuterol, Beclomethasone, Budesonide, Cetirizine, Chlorpheniramine, Cyproheptadine, Dextromethorphan, Diphenhydramine, Fexofenadine, Fluticasone, Guaifenesin, Hydrocodone, Ipratropium, Levocetirizine, Loratadine, Promethazine, Montelukast, Phenylephrine, Pseudoephedrine, Terbutaline.
Miscellaneous	Antidiabetic drugs (Metformin, Insulin), Antidotes (Deferoxamine, Dimercaprol, Edetate); Allopurinol, Aurothioglucose, Colchicine, Penicillamine, Pegloticase; Alendronate, Zoledronic acid; Contrast agents (Diatrizoate, Ethiodized, Ferumoxides, Gadopentetate, Iodipamide, Iodixanol, Iohexol, Iopanoic acid, Iopromide), Gadobutrol, Methacholine; Doxazosin, Prazosin, Finasteride; Naloxone.

*Adapted from sources: United Kingdom Porphyria Medicines Information Service (UKPMIS), Cardiff Porphyria Service, and National Acute Porphyria Service (NAPS); American Porphyria Foundation Drug Database. **Evidence-based drug safety assessment results vary among centers, foundations (e.g., ABRAPO), and expert opinions and are frequently updated according to new experimental and clinical evidence. All cited drugs and therapeutic options have their own risk of adverse events and their own porphyrinogenic-inducing potential. All illicit drugs of abuse and addiction (e.g., marijuana, lysergic acid diethylamide, heroin, amphetamines, ecstasy, crack cocaine, hashish, phencyclidine) and nicotine are considered unsafe and at high risk for acute decompensation in patients with acute hepatic porphyria. ***Drugs with topical preparations are considered safe and can be used in mucous membranes and skin without impairment of integrity.

single intravenous infusion of high doses (up to 12.2 mg/kg). Recurrent use of hemin is associated with chronic inflammatory liver disease. Thus, restricting hemin infusions to moderate or severe neurovisceral attacks and recurrent life-threatening attacks is reasonable^{4,5,30,50,51,52}.

Human hemin presentation as heme arginate (Normosang® 25 mg/mL) has been approved for clinical use in all AHPs with a daily dose of 3 mg per kg for 4 consecutive days. A total daily dose of up to 250 mg is allowed, under careful monitoring. Weekly use of heme arginate may be considered in chronic or refractory presentations and can be extended in each course for up to 14 days. Heme arginate presentations are used in most countries in Europe, Latin America, and South Africa. Despite the well-established use of heme arginate for more than 35 years, it has limited experience in pediatric cases. Clinical efficacy and safety results were obtained after evaluation of more than 100 attacks in South Africa, Sweden, and an open-label phase III study, which revealed marked clinical and biochemical responses the earlier the treatment started during acute attacks^{23,30,45,52}.

An important evaluation issue during acute episodes in recurrent attacks is the presence of perimenstrual symptoms in women of childbearing age. In women with recurrent attacks related to the perimenstrual period, long-acting agonists of luteinizing hormone-releasing hormone (LH-RH) or gonadotropin-releasing hormone (GnRH, gonadorelin analogs) receptors are indicated and can suppress the estrogen effects in heme biosynthesis^{4,21,53}. Liver transplantation in AHPs has been studied by different metabolic centers. Most procedures have been performed in patients with recurrent and severe acute attacks or recurrent attacks without early availability of intravenous heme therapy. Liver transplantation may also be considered a therapeutic option in patients with chronic liver disease associated with AHPs^{47,54}.

New therapeutic options have been studied, bringing more sustained clinical responses for patients with AHP. N-Acetyl-D-Galactosamine (GalNAc)-conjugated small interfering RNA (siRNA)-based therapies have been developed for several inherited disorders, including AHPs, primary hyperoxaluria type 1, hereditary *TTR*-related amyloidosis, and familial hypercholesterolemia^{46,55,56,57}. Givosiran (ALN-AS1; Givlaari™, Alnylam Pharmaceuticals, US) 189 mg/mL has been recently approved by the FDA and the European Medicines Agency (EMA) for the treatment of AHPs. Once-monthly subcutaneous administration of givosiran 2.5 mg/kg promotes a sustained reduction of liver ALAS1 levels by degradation of its mRNA in hepatocytes. Thus, it decreases the production of neurotoxic intermediates ALA and PBG and prevents recurrent attacks and chronic and acute symptoms of AIP. Hepatocytes express a galactose receptor in their surface that enables the recognition of trivalent GalNAc and endocytosis of synthetic

siRNA carrying *ALAS1* sequence, allowing interaction of siRNA with original mRNA in the RNA-induced silencing complex (RISC) and promoting degradation of this mRNA and inhibition of ALAS1 synthesis by gene silencing^{5,58,59}. A randomized, double-blind, placebo-controlled, global, and multicenter study was performed in three clinical phases, initially enrolling patients in a 3:1 givosiran: placebo ratio. Only genetically confirmed AIP patients were included in the initial 6 months of the phase I study. Part A was characterized by a single injection of ascending doses, and Part B involved multiple injections of ascending doses in 23 patients without attacks in the prior 6 months. Part C, with multiple injections, included 17 patients with recurrent attacks, defined as two or more recurrent attacks in the prior 6 months or in hemin prophylaxis over the 6 months before the study start. All 6 patients who received once-monthly intravenous injections of givosiran had sustained reductions in ALAS1 mRNA, ALA, and PBG to normal levels with a 79% decrease in annualized recurrent attack rate at that stage. Four groups receiving monthly or quarterly infusions of givosiran at 2.5 or 5.0 mg/kg were compared regarding safety and tolerability. Patients who completed the 6-month investigation were enrolled in an open-label phase I/II extension study (NCT02949830) for up to 42 months, which evaluated the long-term safety and tolerability of givosiran in adults with AIP^{45,59,60}. New data on givosiran safety and efficacy for AHPs will be available in the ENVISION study (NCT03338816), including patients with AIP, VP, and HCP. Current data, thereby, suggests that givosiran is a key therapeutic option for refractory or recurrent AIP, refractory individuals, or cases without access to hemin therapies as a prophylactic alternative.

CONCLUSIONS

AHPs are inherited metabolic diseases related to heme biosynthesis and associated with broad and heterogeneous clinical presentations, particularly classic acute neurovisceral attacks and, more rarely, chronic skin lesions with photosensitivity. Knowledge of specific clinical, laboratory, and neuroimaging diagnostic clues is critical to the proper and early recognition of AHPs and screening of other family members. Therapies related to the treatment of acute neurovisceral attacks and prophylactic approaches for recurrent episodes have been used in clinical practice with significant success in modifying the natural history of this life-threatening condition. More recently, the approval of a new siRNA-based therapy by the FDA and its clinical impact on the disease course became a key milestone in the history of AHPs. Current data, thereby, suggests that givosiran is a key therapeutic option for recurrent AHPs, refractory individuals, or those without access to hemin therapies as a safe and more effective prophylactic treatment.

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