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Acute hepatic porphyrias: Recommendations for diagnosis and management with real-world examples

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ABSTRACT

Acute hepatic porphyria (AHP) is a group of four rare inherited diseases, each resulting from a deficiency in a distinct enzyme in the heme biosynthetic pathway. Characterized by acute neurovisceral symptoms that may mimic other medical and psychiatric conditions, lack of recognition of the disease often leads to a delay in diagnosis and initiation of effective treatment. Biochemical testing for pathway intermediates that accumulate when the disease is active forms the basis for screening and establishing a diagnosis. Subsequent genetic analysis identifies the pathogenic variant, supporting screening of family members and genetic counseling. Management of AHP involves avoidance of known exogenous and hormonal triggers, symptomatic treatment, and prevention of recurrent attacks. Here we describe six case studies from our own real-world experience to highlight current recommendations and challenges associated with the diagnosis and long-term management of the disease.

1. Introduction

The acute hepatic porphyrias (AHP) are a group of rare genetic diseases resulting from decreased activity of specific enzymes in the heme biosynthetic pathway. Diagnosis is challenging because their neurovisceral symptoms, often occurring as acute attacks, are nonspecific, even when severe, and resemble the symptoms of other more common diseases. Prompt diagnosis and treatment can avoid fatal outcomes or long-term symptoms and neurologic damage [1]. Recommendations have been developed to enable early recognition and treatment of these diseases [1–3] and have been reviewed in detail [4,5]. Here we provide updated recommendations for diagnosis and management as illustrated by case vignettes from our individual experiences and supported by the published literature.

2. Pathophysiology of acute hepatic porphyrias

Heme needed for production of a variety of essential hemoproteins is

Abbreviations: ADP, δ–aminolevulinic acid dehydratase porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; ALAD, δ-aminolevulinic acid dehydrogenase; ALAS1, δ-aminolevulinic acid synthase 1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; COVID, coronavirus disease; CPOX, coproporphyrinogen oxidase gene; Cr, creatinine; CYP, cytochrome P450; ED, emergency department; EEG, electroencephalogram; EPP, erythropoietic protoporphyria; GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase; GnRH, gonadotropin releasing hormone; HBMS, hydroxymethylbilane synthase; HCP, hereditary coproporphyria; HIDA, hepatobiliary iminodiacetic acid; HRQoL, health-related quality of life; ICU, intensive care unit; INR, international normalized ratio; mRNA, messenger RNA; OLE, open-label extension; PBG, porphobilinogen; PBGD, PBG deaminase; PCT, porphyria cutanea tarda; PGC- 1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PPOX, protoporphyrinogen oxidase; RNA, ribonucleic acid; siRNA, small interfering RNA; SIADH, syndrome of inappropriate antidiuretic hormone secretion; VP, variegate porphyria.

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synthesized in all cells in the body by a sequence of eight enzymes (Fig. 1).

The first step in the pathway is catalyzed by the mitochondrial enzyme δ-aminolevulinic acid synthase (ALAS), resulting in condensation of glycine and succinyl-coenzyme A to form δ-aminolevulinic acid (ALA), the first intermediate in the pathway and an amino acid committed exclusively to heme formation. This is the rate-limiting step in heme synthesis, particularly in the liver, where heme exerts negative feedback regulation to control synthesis of ALAS [6]. The ubiquitous form of this enzyme, termed ALAS1, is found in all tissues.

In the porphyrias, various intermediates in the heme biosynthetic pathway accumulate initially in either the liver or the bone marrow. Thus, the individual porphyrias are classified as either hepatic or erythropoietic. Of the five hepatic porphyrias, four are classified as acute because their symptoms result primarily from adverse effects on the nervous system, and the fifth, porphyria cutanea tarda (PCT), manifests as a chronic blistering photosensitivity without neurological symptoms.

Each of the four types of AHP results from an inherited deficiency of a different enzyme in the heme biosynthetic pathway [7,8] (Fig. 1). Distinctive features of AHPs, in contrast to other porphyrias, include a build-up of the porphyrin precursors ALA and porphobilinogen (PBG) and neurological symptoms. AIP (acute intermittent porphyria), the most common of the AHPs, HCP (hereditary coproporphyria) and VP (variegate porphyria) are autosomal dominant inherited disorders with low penetrance [9]. All three may cause similar neurovisceral symptoms, however HCP and especially VP may also cause chronic blistering photosensitivity. ALAD porphyria (ADP), the rarest of the AHPs (~10 documented cases), is due to biallelic variants in *ALAD* which encodes δ-aminolevulinic acid dehydrogenase (ALAD), the second enzyme in the pathway, and elevates ALA and porphyrins, but not PBG. Symptoms of ADP, like ultrarare cases of homozygous AIP, HCP and VP, are often first manifest in childhood [10].

The inherited partial enzyme deficiencies in AIP, HCP and VP become significant when hepatic heme synthesis is stimulated by environmental, nutritional, and hormonal factors causing a deficiency in the 'regulatory heme pool' within hepatocytes and consequently increasing expression of ALAS1. This leads to hepatic accumulation of ALA, PBG, and porphyrinogens [1,2]. ALA and PBG can cross the blood brain barrier and may account for neurotoxic effects in the central, peripheral, and autonomic nervous systems, resulting in acute and chronic symptoms [11,12].

Known triggers of acute porphyric attacks include certain medications, and steroid hormones (especially progesterone), nutritional changes, alcohol, and smoking, which can increase ALAS1 in hepatocytes. Databases are available which categorize drugs according to their level of safety or risk based on currently available evidence, which is often incomplete (https://www.drugs-porphyria.org; https://www.porphyriafoundation.com/drug-database). Increases in progesterone levels cause cyclic attacks in some women during the luteal phase of the menstrual cycle [13].

3. Clinical manifestations

The major manifestations of the AHPs are neurologic, including neuropathic abdominal pain, peripheral neuropathy, and mental disturbances [1]. Severe abdominal pain, the most common symptom, occurs in 85–95% of acute attacks, is usually diffuse rather than localized and often accompanied by nausea, vomiting, distention, constipation, and sometimes diarrhea [1,10]. Its severity may not be appreciated because physical signs such as abdominal tenderness, rebound tenderness and rigidity are absent or mild. Other symptoms include insomnia (often an early symptom), palpitations, seizures,

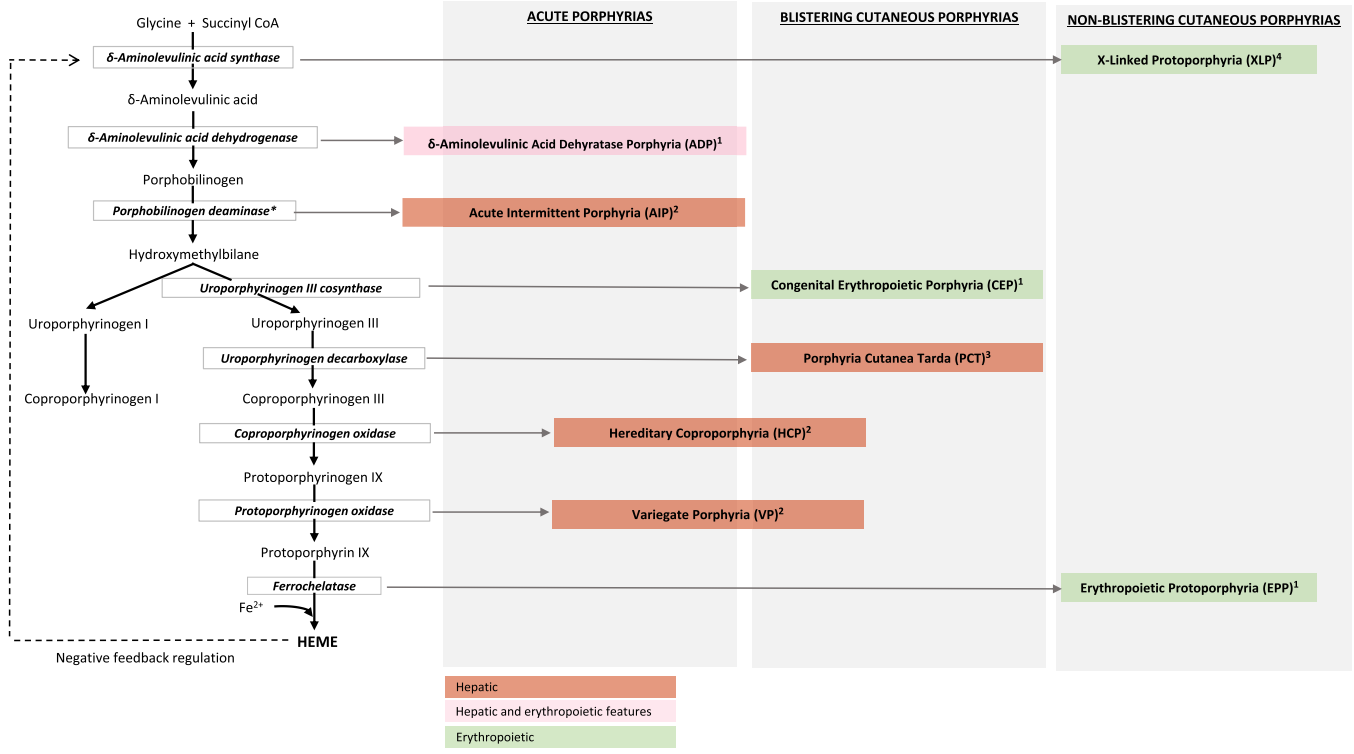

Fig. 1. Intermediates and enzymes of the heme biosynthetic pathway, showing negative feedback regulation of the first and rate-limiting enzyme by the end product heme, and the porphyrias that result from altered activity of each of these eight enzymes. Also shown are the common abbreviations for these porphyrias, their classification as hepatic or erythropoietic or based on their most prominent clinical features, and their modes of inheritance. Note that ADP is not readily classified as hepatic or erythropoietic. PCT is due to an acquired deficiency of hepatic uroporphyrinogen decarboxylase, with a contributing heterozygous mutation of this enzyme in ~20% of cases. [*Porphobilinogen deaminase is also known as hydroxymethylbilane synthase (HBMS)]. [1]Autosomal recessive; [2]Autosomal dominant;[3]Autosomal dominant (~20% of cases);[4]×-linked.

restlessness, hallucinations, and other acute psychiatric symptoms [1]. Hyponatremia may be due to inappropriate antidiuretic hormone secretion or excess gastrointestinal (GI) or renal sodium loss and may precipitate seizures. Although ALA and PBG are colorless, reddish urine due to excess porphyrins or brownish urine due to porphobilin (a degradation product of PBG), occurs in 75% of cases [10]. The clinical characteristics of an acute porphyric attack are similar for each of the acute porphyrias and are generally more common and severe in AIP than in HCP and VP [11,12]. In VP and, rarely, in HCP, the presence of blistering skin lesions often leads to a misdiagnosis of PCT.

4. Diagnosis

The timely diagnosis of AHP allows for early treatment and prevention of morbidity and mortality. Patients often present to the emergency department (ED), which may not consider AHP as a cause of abdominal pain or other symptoms. Although a "classic triad" comprising severe abdominal pain, peripheral neuropathy, and central and autonomic nervous system involvement has been suggested as a focus for testing [2], it is not clear how often this occurs or is recognized. Unexplained abdominal pain should be a major focus for testing for AHP, after an initial workup does not reveal a more common cause.

First-line testing for AHP is simple (spot urine PBG and total porphyrins, normalized to creatinine) and this testing is most likely to be positive when symptoms are present. However, as PBG often remains elevated for a prolonged period after an attack, testing can be diagnostic even if done apart from an acute attack. When found, a substantial PBG elevation is a highly specific diagnostic finding, and establishes without doubt that the patient has AIP, HCP or VP, the 3 most common AHPs. Prompt treatment of newly recognized cases can then follow. ALA can also be measured but does not add sensitivity or specificity to measurement of PBG for diagnosis of AIP, HCP and VP [14]. Measurement of total porphyrins will always detect conditions accompanied by ALAD deficiency, particularly ultrarare cases of ADP, lead poisoning and hereditary tyrosinemia type 1 and cases of HCP and VP tested after PBG (and ALA) levels may have decreased. However, second-line testing is needed to evaluate isolated elevations of porphyrins, which can occur in other medical conditions. Importantly and more frequently, negative results exclude AHPs as the cause of concurrent symptoms and obviate the need for more extensive but less conclusive evaluation later when symptoms may be absent. DNA testing may be part of second-line testing, but because penetrance is low, the finding of an AHP variant alone is insufficient, and biochemical testing is needed to establish a diagnosis of clinically active AHP.

Samples for porphyria testing are almost always sent to outside laboratories, but even delayed results on samples obtained at the time of symptoms can be definitive. Postponed testing causes delay, and results are less definitive if symptoms have resolved. In-house use of a kit for rapid detection of markedly elevated urine PBG concentration [15], which is diagnostic for AIP, HCP or VP, should be encouraged. But because this qualitative method does not normalize results to creatinine (important for dilute samples) or test for increased porphyrins, the same sample should be saved for later quantitative testing for ALA, PBG and porphyrins.

There are no standards for diagnostic biochemical testing for porphyrias in the U.S. and Canada, in contrast to the UK, European Union and Australia. Laboratory methods for PBG and ALA include column chromatography/spectrophotometry and mass spectrometry. Porphyrins are measured using high performance liquid chromatography (HPLC) with fluorescence detection or mass spectrometry [14]. Measurement methods and reference intervals differ among laboratories, making comparison of results difficult. Normalization of urine results to creatinine allows for meaningful monitoring of results over time, although this is not always done, as shown in some of the cases reported here.

4.1. Case 1

A 30-year-old woman recently increased her alcohol intake following a major life stress event and then developed severe abdominal pain, nausea, vomiting and diarrhea. When hospitalized for a suspected intestinal infection, intravenous morphine was required for pain control. Although laboratory testing, abdominal imaging, and upper and lower GI endoscopies did not establish a definite cause for her symptoms, she gradually improved and was discharged after 2 weeks.

The patient was well for about 2 years, when these symptoms recurred resulting in multiple visits to the ED. With one episode, she developed hallucinations and mental status changes and was admitted to a psychiatric unit but then transferred to an ED with abdominal pain, where she had a grand mal seizure associated with hyponatremia. She was admitted to a medical unit with tachycardia (120 beats per minute), hypertension (BP 174/114 mmHg), and disorientation but without focal neurological signs. Workup included ALT 114 U/L (normal range 5–35 U/L), AST 94 U/L (normal range 13–40 U/L), brain MRI with multiple areas of subcortical signal abnormalities, and EEG with recurring single and multiple spike and sharp discharge activity appearing to arise from the left anterior temporal region. A lumbar puncture revealed normal protein and glucose. Intravenous phenytoin was started, after which her abdominal pain worsened. Hyponatremia (116 mEq/L) due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) was attributed to fluoxetine. A hepatobiliary iminodiacetic acid (HIDA) scan was abnormal, so she underwent laparoscopic cholecystectomy with removal of a normal gallbladder. After some improvement, the patient was discharged on phenytoin with diagnoses of alcoholic withdrawal and liver disease likely related to alcohol and was referred for rehabilitation.

Urine porphyrins resulted as "positive" after discharge. However, the patient could not be contacted because after her symptoms had worsened, she traveled to another state to stay with family. She was hospitalized there with abdominal pain and weakness, which progressed to quadriparesis, respiratory failure and aspiration pneumonia. Urinary PBG was 44 mg/24 h (ref 0–4). Phenytoin was stopped and she improved gradually when treated with intravenous glucose. She was discharged for physiotherapy and rehabilitation. The patient recovered almost completely, with some residual painful hyperesthesia of the lower extremities, proximal muscle weakness and impaired short-term memory. She did well, but several attacks, some premenstrual, occurred in the next few years.

Commentary: A diagnosis of AHP was not considered during the patient's initial hospitalization. Recurrent symptoms and additional developments (psychiatric symptoms, seizures, hyponatremia, tachycardia, hypertension, transaminase elevations, brain MRI and EEG abnormalities) eventually prompted suspicion of AHP and a qualitative send-out test for urine porphyrin elevation. However, the index of suspicion was low, and a positive result was returned after she was discharged. An antiseizure drug that is harmful in AHP was started and an unnecessary cholecystectomy performed before discharge. Thus, while it is often important to screen for AHP even if clinical suspicion is low, delayed reporting of results of a send-out test can be problematic. Use of a kit for rapid in- house detection of PBG elevation would have hastened diagnosis and might have led to appropriate treatment of this patient with hemin.

Development of paresis more strongly suggested AHP at a second hospital, and this diagnosis was established by marked elevation in urine PBG. Measurement of urine PBG is the preferred screening test for symptomatic AHP and may be combined with measurement of porphyrins. Collecting a spot sample and normalizing results to creatinine avoids delay from collecting a 24-h urine. This patient's improvement can be attributed to stopping a harmful drug and perhaps treatment with glucose. However, hemin rather than glucose is preferred for treatment of severe attacks.

Recovery can be complete even after severe attacks of AHP, but mild residual effects that persist may have long term consequences. Attacks may recur even in the absence of harmful drugs and if frequent, may require

preventive strategies. Ongoing management should also include genetic analysis, genetic counseling, laboratory monitoring and liver imaging, as will be illustrated by additional cases.

5. Treatment and management recommendations

The four aspects of management of AHP are: 1) Treatment of acute attacks, 2) Recommendations for lifestyle and nutritional modifications and reducing exposure to harmful drugs, 3) Pharmaceutical interventions to prevent frequent attacks and 4) Genetic counseling and family screening.

5.1. Treatment of acute attacks

This should include addressing exacerbating factors, treatment of symptoms, and disease-specific treatment with hemin, which restores hepatic heme homeostasis and reduces overproduction of ALA and PBG. Hospitalization is usually necessary for treatment of severe symptoms, but mild attacks are sometimes manageable in an outpatient setting [2].

5.1.1. Supportive and symptomatic therapy

Medications known to exacerbate AHP should be discontinued or replaced by safe alternatives whenever possible. Hospitalization is usually required for treatment of severe pain, nausea, vomiting, agitation, and other central nervous system manifestations. Management of fluid and electrolyte imbalances such as hyponatremia, assessment of nutritional status, and monitoring for onset of motor and respiratory weakness are important [1,2].

5.1.2. Disease-specific therapy

These approaches are specific because they down-regulate hepatic ALAS1 and reduce excess hepatic production of ALA and PBG.

Carbohydrate loading, by mouth or intravenously, provides nutritional replacement and represses production of excess hepatic ALAS1 [16,17]. This effect is mediated by PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α) [18]. Although relatively weak, this effect may be helpful in the early stages of an attack, especially when dietary restriction has contributed, or while waiting for hemin to become available [1,2]. Carbohydrate is usually administered as intravenous dextrose 10% solution in water or half-normal saline with the goal of delivering 300 to 500 g of glucose per day, while monitoring for hyponatremia is important. Oral glucose polymer solutions may be used if tolerated.

Carbohydrate loading should not be allowed to delay the use of *intravenous hemin,*[1] which is currently considered to be the most effective treatment for acute attacks. In the United States and Canada, hemin is available as a lyophilized hematin preparation (Panhematin®, hemin for injection,[2] Recordati Rare Diseases, Inc., Bridgewater, NJ [19] and Recordati Rare Diseases Canada Inc., Toronto, ON [20]). It has been available in the US since 1983. In Europe and some other countries, hemin is available as heme arginate (Normosang®, also from Recordati Rare Diseases). In North America, the respective regulatory authorities have granted it approval for "the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate" [19,20]. However, experience supports use of hemin without a trial of carbohydrate loading in all types of AHP regardless of the precipitating factors, in men or women and during pregnancy. When administered intravenously, hemin restores the regulatory heme pool in hepatocytes, leading to down-regulation of ALAS1 and reduction in the overproduction of the porphyrin precursors ALA and PBG [11,12,21]. However, the exact mechanism by which hemin ameliorates acute attacks of porphyria has not been elucidated [19,20]. The standard regimen for treatment of an acute attack is 3 to 4 mg/kg/day of hemin daily for 4 days or until symptoms are resolved or clearly improved.

5.2. Recommendations for lifestyle and nutritional modifications and reducing exposure to harmful drugs

Identification and elimination of factors that precipitate or worsen acute attacks is an important aspect of the long-term management of AHP [3]. Patients are counseled to avoid possible precipitating factors such as excessive alcohol use, tobacco, and medications that induce hepatic ALAS1 and CYPs. Caloric restriction to lose weight or from illness may also provoke attacks, and patients often identify psychological stress as contributing to their attacks.

5.2.1. Case 2

A 22-year-old male was referred after a recent hospitalization elsewhere for evaluation of a new diagnosis of AHP. He described a 1-year history of intermittent severe abdominal pain associated with nausea, vomiting, constipation, and reddish urine 2–3 times monthly. These often occurred after use of inhaled cannabis up to 3 g twice daily, which was taken for relief of severe anxiety. One episode followed a period of religious fasting. Hyponatremia (Na 124 mmol/L) and hypertension (150/90 mmHg) were documented at an ED visit 7 months previously. Skin hyperpigmentation of the face and arms, and skin fragility and blistering on his arms and dorsal hands had occurred for the past 10 years, which he had not related to sunlight exposure. A maternal uncle and one of his 3 younger brothers had similar blistering skin symptoms. Evaluation included a normal abdominal and pelvic CT scan and an upper endoscopy that revealed esophagitis and gastritis. Results from an outside laboratory demonstrating marked elevations in urine PBG and urine porphyrins (Table 1) were diagnostic for an acute porphyria. However, the patient left the hospital against medical advice before these results were available.

He was readmitted 10 months later with severe abdominal pain that developed 3 days after he abruptly stopped smoking marijuana but improved somewhat with marijuana use. A random urine PBG was 332 μmol/g creatinine and serum sodium was 130 mmol/L. He was treated with hemin reconstituted with albumin 4 mg/kg IV daily for 4 days in addition to oral glucose and continuous dextrose 5% in water at 125 mL/h for 24 h.

At the porphyria outpatient clinic 4 weeks later, his abdominal pain had improved. Hyperpigmented macules and patches, crusted erosions, and rare fluid-filled vesicles were observed on both dorsal hands. Appropriate lifestyle modifications for AHP were recommended. He gradually discontinued marijuana use over the next several months and had no further attacks.

One year later, the patient had restarted and again abruptly stopped

Table 1
Laboratory results in a 22-year-old male with a diagnosis of AHP.

Analyte	Value	Units	Range
Porphobilinogen	**374**	μmol/day	0–11
Total Porphyrins	–	–	
Uroporphyrin I	**153**	μmol/mol creatinine	0–4
Uroporphyrin III	–	–	
Heptacarboxyl porphyrin	**9**	μmol/mol creatinine	0–2
Hexacarboxyl porphyrin	–	–	
Pentacarboxyl porphyrin	–	–	
Coproporphyrin I	**51**	μmol/mol creatinine	0–6
Coproporphyrin III	**164**	μmol/mol creatinine	0–14

[1] *Hemin is the generic name for all heme preparations used for intravenous administration. Hemin is also a chemical term that refers to the oxidized (ferric) form of heme (iron protoporphyrin IX) and is usually isolated as hemin chloride. In alkaline solution, the chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin.*

[2] *Hemin for injection was known previously as hematin* [19,20].

smoking marijuana while on a trip abroad to visit family, and after 5 days, developed chest and abdominal pain, constipation, and red-colored urine. At our clinic, hemin 4/mg/kg reconstituted with albumin was administered daily for 4 days in the outpatient setting, with complete abatement of symptoms within 3 days. The patient resolved to avoid marijuana entirely. Results of genetic analysis are pending, and the patient was advised to encourage his relatives to be tested once his variant is established.

Commentary: The initial diagnosis of AHP was established by a marked elevation of urine PBG, but the type of AHP remains to be defined. The patient's blistering skin lesions suggest that VP is most likely, but diagnosis of VP requires analysis of plasma and fecal porphyrin analyses and should be followed by genetic testing. This has not yet been accomplished because the patient was again lost to follow up. However, hemin treatment is indicated for treatment of attacks of all AHPs and was appropriate without establishing the type of AHP. Advising patients on lifestyle modification can consider well established exacerbating factors. But whether marijuana use induces hepatic ALAS1 and CYPs and exacerbates AHP is not known. This patient used marijuana for symptom relief and attributed severe attacks to abruptly stopping daily marijuana use. Whether onset and relief of symptoms might have been related to other factors is not known, and some patients have attacks even after known exacerbating factors are addressed. This patient's goal was to stop marijuana use completely, and he was encouraged to do this and monitor for symptom improvement. A survey by the Porphyrias Consortium on the impact of cannabis use in patients with AIP is currently underway.

5.3. Pharmaceutical interventions for prevention of attacks

Most heterozygotes for pathogenic AHP variants never develop symptoms. Some individuals experience only one or a few acute attacks in their lifetimes. However, a small subset suffers from frequently recurring attacks even after known harmful factors are removed. Pharmaceutical interventions are available and important for such patients but their use benefits from expert experience.

5.3.1. Gonadotropin-releasing hormone (GnRH) analogues

Some women with AHP develop frequent cyclic attacks during the luteal phase when progesterone levels are high. Suppression of ovulation by treatment with a GnRH analogue may prevent such attacks [13]. After success in preventing attacks is demonstrated, one option is to add a low dose estradiol skin patch after several months to prevent menopausal symptoms and bone loss [3].

5.3.2. Hemin prophylaxis

Hemin is short-acting and is administered as a daily infusion for 4 or more days to treat acute attacks of AHP. However, it can also prevent attacks if given weekly or even twice weekly, as described in case reports [21–24] and a clinical practice survey [25]. Prophylaxis entails giving scheduled infusions in the absence of symptoms, and if successful, the need for ongoing hemin prophylaxis can be reassessed by interrupting treatment after 6–12 months [1,3]. An alternative is to provide a single hemin infusion "on demand" when symptoms begin and thereby abort an attack and avoid hospitalization and a full course of hemin treatment [1,3]. This approach requires that an infusion facility be available to administer hemin on short notice.

5.3.2.1. Case 3. A 30-year-old male developed intermittent abdominal pain, nausea, anorexia, and other GI symptoms resulting in multiple ED visits. Headaches and severe eye and facial pain also occurred 2–3 times monthly but were not associated with his abdominal symptoms. Extensive laboratory investigations and CT imaging of the head were unrevealing. Upper GI endoscopy revealed mild distal esophagitis. He was hospitalized at age 37 with severe abdominal pain for 2 days due to acute idiopathic pancreatitis with elevation in serum lipase (7939 U/L, ULN 82 U/L) and amylase (309 U/L, ULN 105 U/L), and mild edema of the pancreatic tail by CT imaging. He improved but after returning home, abdominal pain recurred frequently without evidence of pancreatitis or abnormal findings by extensive abdominal imaging (MRI/MRCP/CT/US). He reported his mother had elevated urine porphyrins in the past, but details were unavailable, and there was no definite family history of porphyria. He was tested for porphyria at age 39, revealing modest elevation in urine PBG and marked elevation in urine porphyrins consisting almost entirely of coproporphyrin III (Table 2). Erythrocyte PBG deaminase activity was normal (3.08 mU/gHb, normal range 2.10–4.30), providing evidence against AIP. A fecal sample was insufficient for porphyrin analysis. Genetic analysis revealed a known pathogenic *CPOX* variant c.995G > A (p. Arg332Gln), which established a diagnosis of HCP. He was advised to avoid exacerbating factors for AHP.

Hemin infusion 4 mg/kg/day (reconstituted in 25% albumin) for 5–14 days was recommended for acute treatment of recurrent episodes of abdominal pain, nausea, and vomiting, along with recommendations to avoid exposure to exacerbating factors and sunlight. Although there was some decrease in symptomatology with hemin infusions, the patient continued to complain of persistent GI symptoms, prompting the use of weekly hemin therapy for one month. Notably, the patient developed rapid onset of painful erythema of his arm and induration and swelling at the injection site with these hemin infusions, even when the infusion rate was decreased and despite use of albumin as a diluent. Subsequently, a port was placed for continued prophylactic hemin infusions with marked improvement in abdominal cramps. He continues to receive monthly hemin treatment. A baseline abdominal ultrasound showed no evidence of hepatocellular carcinoma (HCC). Monitoring for iron overload and annual follow-up for HCC was recommended. The patient opted for further follow-up locally. The patient was unwilling to try givosiran (see Section 5.3.3) as he objected to COVID mRNA vaccines and, despite education, extended this objection to siRNA therapy.

Commentary: The urine findings in this case are typical of HCP, with modest elevation in urine PBG and marked elevation of coproporphyrin III. However, elevations in PBG and porphyrins are quite variable in all AHPs, and these urine findings are not specific for HCP. An HCP diagnosis can be established by finding a marked elevation in total fecal porphyrins that is accounted for almost entirely by coproporphyrin III, with elevation in the coproporphyrin III/I ratio and much less elevation in protoporphyrin (VP is distinguished from HCP by plasma porphyrin scanning and approximately equal elevations in fecal coproporphyrin and protoporphyrin.). The diagnosis was established in this case by genetic analysis and demonstrating a previously described pathogenic CPOX variant. Identification of this familial variant facilitates screening relatives and genetic counseling.

Timely treatment of attacks with hemin is important in all AHPs, and in men as well as women [1,2]. *Product labelling* [19,20] *specifies that intravenous hemin should be reconstituted in sterile water immediately before use as it contains no preservatives and undergoes rapid degradation in solution. Degradation products can cause infusion site phlebitis, especially if small peripheral veins are used, and a transient thrombocytopenia and coagulopathy may develop* [26,27]. *Reconstitution of hemin with 25% albumin* [28]

Table 2
Laboratory results in a 39-year-old male with HCP.

Analyte	Value	Units	ULN
Porphobilinogen	**2.0**	mg/24 h	0.34
Total Porphyrins	**1523**	μg/24 h	210.7
Uroporphyrin I	47	"	22.4
Uroporphyrin III	16	"	7.4
Heptacarboxylporphyrin	5	"	3.3
Hexacarboxylporphyrin	–	"	?
Pentacarboxylporphyrin	11.7	"	4.6
Coproporphyrin I	87	"	48.7
Coproporphyrin III	**1356**	"	148.5

ULN: Upper Limit of Normal

and prior experience of the pharmacy and nursing staff can avoid these consequences. As in this case, use of an intravenous port can minimize adverse effects of more long-term prophylactic hemin. Other uncommon side effects of hemin may include fever and headache. Nephrotoxicity [29] *and hepatotoxicity* [30] *have been reported with unintended excessively high doses of hemin. Iron overload may occur with repeated hemin infusions,*[3] *although its frequency is unknown. Monitoring of serum ferritin is recommended in patients receiving multiple hemin treatments. However, infusion of hemin is followed by an acute increase in ferritin of unknown duration that is part of an acute phase response and may not necessarily indicate iron overload. Iron overload confirmed by other methods, such as MRI can be treated by phlebotomy* [31]. *Iron chelators can alter hepatic iron homeostasis and worsen porphyria in laboratory models, and their safety in human AHP is not established.*

5.3.3. siRNA interference therapy

Small interfering ribonucleic acids (siRNAs) are short RNA fragments that target and bind to specific sequences on messenger RNA (mRNA), leading to their destruction. Consequently, the siRNA specifically downregulates the formation of selected mRNAs and their protein products [32].

Givosiran (Givlaari®, Alnylam Pharmaceuticals Inc., Cambridge, MA) is a subcutaneously administered siRNA interference therapeutic and first in this class to be approved for the treatment of AHP in adults in the USA [33], Canada [34] and Brazil [35] and in adults and adolescents aged 12 years and older in the European Economic Area, United Kingdom, Switzerland, and Japan [36]. By targeting mRNA encoding ALAS1, givosiran lowers ALAS1 expression, thereby reducing hepatic production and accumulation of ALA and PBG [32,37]. Regulatory approval was based on the results of Phase I/II studies [37,38] and a randomized, double-blind, placebo-controlled, multinational phase III study (ENVISION) [39]. The phase III trial was a 36-month study in which the efficacy and safety of givosiran in patients with AHP was evaluated during a 6-month, double-blind, randomized, placebo-controlled period followed by a 30-month open label extension (OLE) period. A total of 94 patients (89 AIP, 1 HCP, 2 VP, 2 with AHP type unidentified but suspected AIP) were randomly assigned to monthly givosiran (at a dose of 2.5 mg per kg of body weight) or placebo for the first 6 months. A 74% reduction in the mean annualized attack rate, reduction in the biochemical markers ALA and PBG (86% and 91% respectively), fewer hemin infusions (54% in the givosiran group did not require hemin use versus 23% in the placebo group), and reduction in physical pain and limitations were observed in the givosiran group versus the placebo group after 6 months. Key adverse events that were observed more frequently in the givosiran group were elevations in serum aminotransferase levels, changes in serum creatinine levels and the estimated glomerular filtration rate, and injection-site reactions [39].

A *post-hoc* analysis of the ENVISION data demonstrated reduction in the number and severity of attacks, days with worst pain scores above baseline, and opioid use versus placebo [40].

A 24-month interim analysis of patients who continued in the OLE has been published [41]. Patients initially received either 1.25 or 2.5 mg/kg body weight monthly, but the lower dose was increased to 2.5 mg/kg body weight at or after the 13-month visit due to inadequate disease control. Consistent with the results from the double-blind period, long-term givosiran was associated with a continuous and sustained reduction in annualized attack rate and hemin use (68% of givosiran and 49% of placebo crossover patients did not require supplemental hemin). Lower opioid use and improvements in several patient-reported outcomes were observed [41].

Based on these aggregate data, current labelling [33,34,36] indicates givosiran should be administered subcutaneously at a dose of 2.5 mg/kg body weight once monthly. Monitoring of hepatic function, renal function, and homocysteine levels is recommended [33,34,36]. It has been further suggested that it is good practice for a random urine to be sent for ALA, PBG, total porphyrins, and creatinine at follow-up visits [42].

5.3.3.1. *Case 4.*

A 40-year-old female of Mexican descent was referred to our clinic for management of previously diagnosed AIP. Recurrent attacks of abdominal pain and other symptoms began in her late teens, one prompting surgery for suspected appendicitis and removal of a normal appendix. An attack in her twenties progressed to paralysis and respiratory failure requiring intubation and treatment in the ICU for one month. AHP was confirmed by PBG testing (results not available). She responded slowly to treatment with hemin followed by physiotherapy and rehabilitation for several months. Subsequently a heterozygous pathogenic *HMBS* variant [c.457C > T (p.Q153*)] confirmed a diagnosis of AIP. After several more attacks, including one requiring ICU care, she developed a permanent mild motor neuropathy and mild chronic renal failure. She was then followed at different centers in the U.S. and Europe and had at least one attack with a PBG level of 95.1 μmol /L (ref 0–8.8). Treatment with givosiran was started approximately 3 years prior to her first visit to our clinic. She had no further attacks during that period.

On our initial evaluation, the patient reported periods of prolonged fasting and low carbohydrate intake, often followed by abdominal discomfort, confusion, and bad dreams, especially during the luteal phase of the menstrual cycle. These symptoms were less frequent after nutritional counseling. An acute attack with severe abdominal pain and other symptoms developed several days after the first dose of a COVID mRNA vaccine. Her symptoms worsened during initial treatment at home with carbohydrate loading for several days, including fatigue, headache, nausea, allodynia and pain and distal lower extremity weakness. She was hospitalized and her symptoms responded to treatment with hemin (reconstituted with sterile water) 3 mg/kg daily for 3 days. She developed transient thrombocytopenia (nadir at 82 × 10*9/L) and mild INR elevation (1.4) that resolved within a few days. Urine PBG measured after the first hemin infusion was normal (0.6 μmol/mmol creatinine, ref. <1.5). A similar attack followed a second dose of the COVID mRNA vaccine and was also treated with hemin, although PBG levels were again normal (below detection limits; measured at a different laboratory). The patient remains well on givosiran, but with mild chronic kidney disease (CKD), hypertension, anemia, motor neuropathy and mild elevation of serum homocysteine (22 umol/L, ref. 4–10 μmol/L). Nutritional follow-up continues, and she has recently started treatment to lower homocysteine levels.

Commentary: As in other cases reported here, there was a long delay between the onset of the first symptoms and episodes and diagnosis of AHP, which was only made once the patient was already hospitalized and intubated, with paralysis and respiratory failure. This contributed to her lingering neuropathy and highlights the importance of rapid diagnosis and treatment. The case also highlights the importance of baseline management, which includes nutritional optimization and avoidance of triggers, best achieved with regular medical visits when these points can be emphasized, and patient comprehension can be verified. Temporary loss of medical follow up led to these elements being suboptimal, in this case.

Givosiran treatment significantly reduced the frequency of attacks. However, occasional "break-through "attacks of the same symptoms still occurred and were treated as in the past with hemin, although subsequent ALA and PBG results showed no definite elevations. There was a close temporal association between mRNA COVID-19 vaccination and acute episodes in this case, with no other identifiable triggers; however, no causality can be established, and it should be emphasized that COVID-19 vaccination is recommended for all AHP patients and has been given without consequences to many. Her symptoms improved with hemin treatment, even though her PBG levels were not elevated. Although these symptomatic episodes may have been due to other causes, it is also possible that in patients with a long history of frequent attacks other neurological mechanisms may become established that

[3] 1 mg hemin contains 0.086 mg of iron. (data on file)

cause recurrent symptoms even in the absence of ALA and PBG elevation. While it is clear that givosiran is highly effective in preventing frequent attacks of AHP, episodes of acute symptoms may not be completely prevented and in some cases, as reported here and elsewhere by others [43]*, may be associated with little or no ALA and PBG elevation.*

This case also illustrates that management of AHP should include attention to long term complications such as hypertension and CKD. Decreased renal function is a known consequence of AHP, but in the phase III trial of givosiran, increases in serum creatinine were greater with givosiran than with placebo [39,41] *and a transient decrease in renal function in patients treated with givosiran has been reported elsewhere* [44]*. Although it is not yet clear how significant or durable this effect may be, renal function should be monitored during givosiran treatment. Elevated homocysteine levels may occur in AHP patients and may increase further during treatment with givosiran* [33,41,45,46]*. Some studies suggest that hyperhomocysteinemia increases the risk of cardiovascular disease* [45,46]*. Thus, measurement of blood homocysteine levels prior to initiating givosiran and monitoring for changes during treatment are recommended* [33,34,36].

5.3.3.2. Case 5. A 36-year-old male with a diagnosis of AIP attended our clinic for consultation on management options. He first presented to an outside hospital at age 32 complaining of severe abdominal pain, nausea, and vomiting. Development of severe muscle weakness required admission to the ICU where he was intubated. Electromyography results led to an initial diagnosis of amyotrophic lateral sclerosis. However, after 6 weeks in the ICU, observation of dark colored urine led to suspicion of AHP, and urine PBG was significantly elevated (671.8 μmol/L, ref. 0–8.8), confirming the diagnosis. Hyponatremia (Na 132 mmol/L) and elevated transaminases (AST 88 U/L and ALT 95 U/L) were also consistent with the diagnosis. Molecular testing at a later time point revealed a pathogenic *HMBS* variant (p.Arg26Cys). He was treated with hemin (4 mg/kg/day) and his symptoms slowly improved. Following 6 months in the hospital and 3 months in rehabilitation, he returned home in a wheelchair. He was able to ambulate without support 6 months later (more than one year after the initial attack) with some residual muscle weakness. Chronic pain, daily nausea and vomiting or retching, fatigue, and inability to concentrate continued.

Treatment with givosiran was initiated at the recommended dose of 2.5 mg/kg sc monthly with incomplete improvement in his chronic symptoms. Urinary levels of ALA and PBG decreased but not to normal and seemed to increase with worsening symptoms, especially about one week before the next dose of givosiran. Hemin was required to treat break-through attacks with more severe symptoms every 2–3 months. Two years after starting givosiran, the frequency of givosiran administration was increased to every 3 weeks. This resulted in some clinical improvement and a decrease in attack frequency, but chronic symptoms persisted and urinary PBG levels decreased but were not normalized (Table 3).

After treatment with givosiran every 3 weeks for 9 months, daily nausea, retching or vomiting as well as chronic pain continued. He was unable to work, and his quality of life was poor. Therefore, administration of prophylactic hemin was initiated via a port at 4 mg/kg on 2 consecutive days one week after each givosiran injection. After 4 months, he reported that daily retching, nausea, and vomiting were less frequent and severe. Further break through acute attacks requiring additional hemin have not occurred. PBG results were insufficient to demonstrate a biochemical response to hemin, and additional observation and perhaps elective interruption of treatment will be necessary to determine ongoing benefits of these treatments.

Commentary: As with the previous case, givosiran treatment was associated with a substantial reduction in the levels of urinary PBG. However, break-through attacks and ongoing symptoms were experienced over the course of givosiran treatment despite shortening the interval between givosiran injections. For this patient, addition of prophylactic hemin to the givosiran regimen provided some additional clinical benefit.

Table 3
PBG levels in a 36-year-old male with AIP treated with givosiran and prophylactic hemin. Givosiran was administered every 4 weeks beginning in July 2020. PBG levels were reduced by givosiran, but never normalized. Hemin was required to treat breakthrough attacks every 2–3 months. Givosiran administration was increased from q4 to q3 weekly in 2022 because of ongoing symptoms. After 9 months, prophylactic hemin was initiated in December 2022 and administered on 2 consecutive days one week after the q3 weekly givosiran injection to help reduce ongoing symptoms and recurrent attacks.

Date	2019	2021		2022						2023								
	09/09	09/28	12/14	01/09	08/30	09/16	12/13	12/ 20	12/ 21	12/ 22	01/03	01/10	01/11	01/12	01/19	01/24	01/31	02/01	02/14
Time (days)	0	751	828	854	1087	1104	1192	1199	1200	1201	1213	1220	1221	1222	1229	1234	1241	1242	1255
Givosiran 2.5 mg/kg (√)				√			√				√					√			√
Hemin 4 mg/kg iv (×)								×	×			×	×				×	×	
Urine PBG (μmol/L)[a]	671.8[#]	311	154	19.3	36.1	17.7	69.4	–	–	10.6	–	–	–	–	–	–	–	–	–
(ref 0–8.8)																			
Urine creatinine (mg/24 h)[a]	192[#]	–	–	984	2690	1866	2080			1647	–	–	–	–	–	–	–	–	–
(ref 1000–2500)																			
Urine PBG (mg/24 h)[b]	–	–	–	–	–	–	–	–	–	–	14	–	–	8.7	15	–	–	–	15.3
(ref 0–0.34)																			
Urine PBG (μmol/g creatinine)[c]	**615.2**[#]	–	–	**47.1**	**22.2**	**43.2**	**39.2**			**29.4**	**33.2**[*]	–	–	**20.8**[*]	**35.6**[*]	–	–	–	**36.3**[*]

PBG: porphobilinogen.
[a] Values from an initial laboratory which also measured creatinine concentration and reported PBG in μmol/L as well as in μmol/g creatinine (last row).
[b] Values from a second laboratory chosen in 2023 by the patient's insurer and reported as mg/24 h without normalization to creatinine.
[c] Values normalized to creatinine, which for samples in 2023* were calculated based on an average creatinine output of 1853 mg/24 h as determined from samples collected in 2022.
[#] Random urine sample as opposed to 24 h collection.

This case also highlights challenges in interpreting laboratory results from different laboratories and with different reference ranges and units of measurement. This patient's insurer switched testing support to a different laboratory in 2023 at the time prophylactic hemin was initiated, and thereafter, urinary PBG levels were reported as mg/24 h, and collections may sometimes have been incomplete, and without normalizing to creatinine. Normalizing urinary PBG to creatinine provides a more reliable measure and allows for better comparison of results over time as it accounts for variation in hydration and incomplete 24 h urine collections.

5.3.3.3. Case 6. At age 21, an African American female began having episodes of abdominal pain, nausea and vomiting at intervals of 1–3 months that were associated with the luteal phase of the menstrual cycle or excess alcohol intake. On the last of several ED visits over 8 months, she reported 5 days of severe abdominal pain with nausea, vomiting, constipation, and fatigue. Findings in the ED included lethargy, tachycardia, hypertension, hyponatremia, elevated creatinine, reduced GFR, hypercalcemia, elevated AST and ALT and leukopenia. "Psychiatric issues", possibly related to the death of her mother 2 years previously, were considered and inpatient psychiatric care was recommended. However, a psychiatrist found no evidence of psychiatric illness, and suggested the medical team should determine the etiology of her abdominal pain and associated metabolic findings. After some improvement, she was discharged, and outpatient workup was planned to rule out porphyria, G6PD deficiency and hemoglobinopathies. A diagnosis of AHP was established as an outpatient by her primary care physician.

The patient continued to have recurrent attacks while feeling well between attacks. She felt that glucose tablets taken when symptoms began were of some benefit. Three attacks required hospital admission and treatment with hemin, which hastened recovery. After relocation to our state for a new job, she was admitted to our hospital twice for treatment of attacks, both starting near the end of a menstrual cycle and without excess alcohol intake. The diagnosis of AIP was documented by biochemical (Table 4) and genetic testing.

The patient was treated with intravenous opioids for severe pain, ondansetron for nausea and vomiting, and hemin 4 mg/kg daily (for 4 or 7 days) reconstituted with human albumin and recovered both times. Given the frequency and severity of her attacks, treatment with givosiran 2.5 mg/kg sc monthly was initiated to prevent attacks. Efforts to maintain 28-day intervals of treatment were not always successful due to insurance issues. As shown in Table 5, the patient received 7 doses of givosiran at intervals of 27–38 days. She was hospitalized with a breakthrough attack without elevation of PBG and recovered after treatment that included hemin and opioids. Abdominal pain recurred, again without elevation of ALA, PBG or porphyrins, after 2 consecutive dosage intervals had to be lengthened to 35–38 days. On-demand treatment with hemin has been added to her outpatient regimen to abort future breakthrough attacks.

Commentary: This case, and others described here, illustrate that repeated acute attacks and ED visits are common before a diagnosis of AHP is made. Suspicion of psychiatric conditions and "secondary gain" are reinforced by multiple recurrences. Abdominal pain is a frequent and difficult diagnostic problem, and a cause is often not established in clinical practice. If an initial evaluation does not establish a diagnosis, first-line testing for AHP to include urine PBG should be part of continued evaluation, even if that diagnosis is not strongly suspected. AHP was considered in this patient, but testing was planned for a later outpatient visit, perhaps because special expertise was considered to be needed for such testing, although this is not the case.

*Attacks are accompanied by severe symptoms that generally require hospitalization and treatment with opioids and antiemetics, and correction of dehydration and electrolyte imbalances. Hyponatremia may be due in part to SIADH. Hypercalcemia may occur particularly in patients with advanced paresis. Specific treatments that down-regulate hepatic ALAS1, include carbohydrate loading, which should only be used for mild attacks, hemin, which is standard treatment for acute attacks, and givosiran, which is effective in preventing frequently recurring attacks. Hemin can also be used for prevention or for early "on-demand" treatment to abort attacks. Iron overload can occur after repeated hemin administration, but elevated ferritin levels within 1–2 weeks of hemin administration may represent an acute phase response rather than iron overload. Recommended monitoring during givosiran treatment is as shown in*Table 5*. As in this case, insurance and scheduling issues can interfere with monthly dosing with givosiran and obtaining recommended laboratory testing, and breakthrough attacks can occur without elevations in ALA, PBG and porphyrins.*

Table 4
Biochemical confirmation of a diagnosis of AIP in this case (abnormal results highlighted and interpreted).

	Patient results	Units	Range
Urine			
Delta-aminolevulinic acid (ALA)[1]	**45.0**	mg/g creatinine	0–7
Porphobilinogen (PBG)[1]	**67.3**	mg/g creatinine	0–4
Total Porphyrins[2]	**2295**	nmol/g creatinine	0–300
Plasma			
Total porphyrins[3]	**5.0**	mcg/dl	0–0.9
Fluorescence peak at neutral pH	**619**	nm	no peak
Erythrocytes			
Porphobilinogen deaminase[4]	**16**	nmol/mlRBC/h	20–50
Protoporphyrin[5]	**341**	mcg/dL	20-80
Zinc protoporphyrin	83	% of total	>50%
Metal-free protoporphyrin	17	% of total	<50%

Interpretation:
[1] Increases in urinary ALA and PBG are diagnostic for AIP, HCP or VP.
[2] Urinary porphyrins are increased with an increased proportion of uroporphyrin (not shown), which can be seen in any of these acute porphyrias.
[3] Plasma total porphyrins are elevated, as can occur in active stages of acute porphyria. The fluorescence peak at 619 nm is consistent with AIP and several other types of porphyria, and strong evidence against VP (peak at ~626 nm).
[4] Erythrocyte PBG deaminase activity is low, as found in most patients with AIP.
[5] Elevation in erythrocyte protoporphyrin with a predominance of zinc protoporphyrin, a nonspecific finding that can occur in active cases of acute porphyrias, but also in iron deficiency and other erythrocyte disorders.

5.4. Genetic counseling and family screening

When a patient is diagnosed with AHP, it is important that they be referred to a specialist with porphyria expertise for genetic counseling to learn more about their condition and how it can affect their families, including their children. Once the type of AHP and a pathogenic variant have been identified, screening of all first-degree relatives for that variant (targeted gene mutation analysis) should be offered [2,3]. Genetic testing programs that are subsidized or free-of-cost [47] can sometimes be accessed for testing of relatives. All heterozygotes should receive appropriate genetic counseling about symptom risk and inheritance. In general, pregnancy is usually well tolerated.

6. Conclusions

It is well established that individuals with symptomatic AHP experience a significant reduction in their health-related quality of life (HRQoL) due to both severe acute attacks and chronic symptoms [48–56]. Symptoms and their negative impacts on daily life include pain and discomfort, anxiety, depression, impaired stress management, sleep disturbances, and inability to work. These long-term consequences of AHP may be at least partially mitigated by timely diagnosis and treatment and adherence to recommendations for long-term management. Delay in diagnosis occurred in all six cases presented here and could have been avoided by a higher index of suspicion or earlier inclusion of PBG testing as part of the workup of symptoms such as abdominal pain.

Table 5

Levels of heme precursors and other selected laboratory values in a 24-year-old female with AIP treated with hemin for 3 acute attacks (4–7 daily doses) and givosiran for attack prevention (7 monthly doses). Values out of range are in bold font. Substantial elevations of urine ALA, PBG and total porphyrins were reduced to normal with givosiran, and these remained normal even with breakthrough symptoms. Urine results were much less variable when normalized to creatine (highlighted) than when expressed per L, reflecting large variations over time in urine creatinine concentrations (0.86 to 3.96 g/L). The patient was initially iron deficient (ferritin 5.6 with microcytic anemia). The later ferritin of 1570 ng/mL likely represents an acute phase response to recent hemin administration rather than iron overload. Serum creatinine, ALT and AST have not increased significantly with givosiran treatment, and amylase and lipase have remained normal, and these continue to be monitored during givosiran treatment. Serum homocysteine has been elevated on givosiran and decreased to normal transiently after hemin treatment.

Time since presentation (days)		0	10	38	54	60	73	105	133	160	176	189	227	262		
Hospitalizations for attacks (duration)		**6 days**			**7 days**						**6 days**					
Hemin 4 mg/kg daily doses (number)		**4**			**7**						**4**					
Givosiran dosing 2.5 mg/kg (√)							√	√	√	√		√	√	√		
Interval between dosing (days)							**Start**	**32**	**28**	**27**		**29**	**38**	**35**		
	Units														**SD**	**Range**
Urine δ-aminolevulinic acid (ALA):	mg/L	74.7	12.9	93.9	–	–	20.9	–	–	7.1	2.8	2.2	4.2	5.7	33	Indeterminate
	mg/g creatinine	**45.0**	**9.8**	**32.4**	**–**	**–**	**24.3**	**–**	**–**	1.5	1.0	0.9	1.1	1.4	16	0–7
	mg/24 h	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**		0–7
Urine porphobilinogen (PBG):	mg/L	111.7	28.5	113.0	–	–	37.2	–	–	6.9	3.2	2.9	7.3	7.8	43	Indeterminate
	mg/g creatinine	**67.3**	**21.8**	**39.0**	**–**	**–**	**43.2**	**–**	**–**	1.4	1.1	1.2	1.9	2.0	23	0–7
	mg/24 h	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**		0–4
Urine total porphyrins:	nmol/L	3809	1171	3977	–	–	898	–	–	373	232	117	419	333	1443	Indeterminate
	nmol/g creatinine	**2295**	**894**	**1371**	**–**	**–**	**1044**	**–**	**–**	78	82	49	111	84	750	0–300
	nmol/24 h	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**		0–300
Urine creatinine:	g/L	1.66	1.31	2.90	–	–	0.86	–	–	4.81	2.84	2.37	3.78	3.96	1.24	–
Serum ferritin	ng/mL	5.6	–	–	–	1,570	–	–	–	–	–	–	–	–		6-137
Serum creatinine	mg/dL	**1.20**	0.91	–	**1.38**	–	–	–	**1.17**	**1.33**	**1.59**	**1.24**	**1.24**	**1.57**	–	0.5–1.04
Serum alanine transaminase (ALT)	U/L	13	21	–	20	–	**43**	–	13	22	40	29	35	22	–	5–35
Serum aspartate transaminase (AST)	U/L	38	**41**	–	**41**	–	**95**	–	31	40	**71**	**42**	**66**	**48**	–	13–40
Serum amylase	U/L	–	–	–	–	–	–	–	–	88	–	101	88	74	–	35–110
Serum lipase	U/L	–	–	–	–	–	–	–	–	72	–	151	62	65	–	0–220
Serum homocysteine	umol/L	–	–	–	–	–	–	–	**46.6**	**>100**	–	22.1	**>100**	**>100**	–	4.7–12.6

Severe acute attacks usually require hospitalization for treatment with hemin 3–4 mg/kg intravenously daily for 4 days or longer, until improvement occurs. Hospitalization also facilitates treatment of severe pain and GI symptoms and prompt detection and management of electrolyte imbalances and neurological manifestations. Although hemin is short-acting, it is also commonly used for preventing frequently recurring attacks [57] and may be given at weekly intervals. Givosiran is long-acting, can be given monthly and is recommended for preventing frequent attacks (typically 4 or more per year) [57]. GnRH analogues are effective in some women with attacks that recur frequently during the luteal phase of the menstrual cycle. Because all of these prophylactic treatments are complicated, consultation in advance with a porphyria expert center is recommended. Cases 3, 4, 5 and 6 presented in this publication provide examples of real-world experience with preventative strategies using hemin or givosiran. The latter three cases illustrate that although givosiran treatment can substantially reduce attack frequency and reduce or normalize ALA and PBG levels, some ongoing symptoms or break-through attacks occur that may not be associated with marked increases in ALA and PBG and be responsive to treatment with hemin. Others have reported similar findings [43]. Further, patient experiences described here are consistent with observations in the givosiran ENVISION study [39,41] where treatment with givosiran reduced, but did not eliminate, attacks or the need for hemin. The pathological mechanism underlying these break-through attacks in the presence of ALAS1 silencing is unknown. Such “break-through attacks without biochemical evidence” certainly question what we know thus far about the mechanism of porphyria attacks and suggest that there may be neuroregulatory factors other than ALA or PBG that play a causative role in these symptoms. This is an avenue for future research in the acute porphyrias.

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Declaration of Competing Interest

None.

Data availability

The data that has been used is confidential.

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