

Update on the diagnosis and management of the autosomal dominant acute hepatic porphyrias

Danja Schulenburg-Brand ¹, Felicity Stewart,² Penelope Stein,³ David Rees,^{3,4} Mike Badminton¹

¹Medical Biochemistry and Immunology, University Hospital of Wales Healthcare NHS Trust, Cardiff, UK

²School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

³Haematological Medicine, King's College London, London, UK

⁴School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

Correspondence to

Dr Danja Schulenburg-Brand, Medical Biochemistry and Immunology, University Hospital of Wales Healthcare NHS Trust, Cardiff CF14 4XW, UK; Danja.Schulenburg-brand@wales.nhs.uk

Received 21 October 2021

Accepted 4 May 2022

Published Online First

18 May 2022

ABSTRACT

The autosomal dominant acute hepatic porphyrias (AHPs), acute intermittent porphyria, hereditary coproporphyria (HCP) and variegate porphyria (VP), are low penetrance adult onset disorders caused by partial deficiency of enzymes of haem biosynthesis. All are associated with acute neurovisceral attacks, which are a consequence of the increased hepatic demand for haem triggered by hormones, stress, drugs or systemic infections which leads to upregulation of the pathway and overproduction of haem precursors 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG). Acute episodes are characterised by severe abdominal pain, nausea, vomiting, hyponatraemia, hypertension and tachycardia, behavioural disturbance and can progress to include seizures, peripheral motor neuropathy and posterior reversible encephalopathy syndrome if undiagnosed and untreated. VP and HCP may also present with photodermatitis skin lesions either alone or during acute symptoms. Diagnosis involves demonstrating increased excretion of PBG in urine. Treatment focuses on removing or managing triggers, supportive treatment and suppressing the hepatic haem pathway by administering human haemin. Chronic complications include hypertension, chronic kidney disease and hepatocellular carcinoma. A small proportion of symptomatic patients with AHP progress to repeated acute attacks which require preventative therapy. A new RNA interference therapy has recently been licensed and is likely to become the treatment of choice in this situation.

INTRODUCTION

The porphyrias are a group of rare, mostly inherited metabolic diseases that are due to deficient function of specific enzymes in the haem biosynthetic pathway (figure 1), apart from X-linked erythropoietic protoporphyria, which is due to gain of enzyme function (figure 1).¹ The clinical manifestations of acute neurovisceral ‘attacks’, photosensitive skin disease or both are the result of accumulation of either porphyrin precursors, 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG) or the porphyrin intermediates of haem biosynthesis.²

Haem (iron protoporphyrin IX) is a prosthetic group in many proteins which have essential cellular functions. Haem is synthesised in all nucleated cells, with approximately 80%–90% produced in the bone marrow for haemoglobinisation of developing red cells and the majority of the remainder in the liver for cytochrome P450 (CYP) enzyme production.² Two isoforms of the first enzyme

in the pathway, ALA synthase (ALAS), are key to regulating haem biosynthesis. In bone marrow, erythroid-specific ALAS2 activity is closely coupled to globin chain production and iron availability. In the liver, ALAS1 is under negative feedback control from the free haem pool, which is dependent on the turnover and demand for haem proteins.²

The porphyrias are classified either pathophysiologically (‘erythropoietic’ or ‘hepatic’) or clinically (‘acute’ or ‘cutaneous’). The acute hepatic porphyrias (AHPs) comprise four disorders in which acute neurovisceral attacks occur: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), which are autosomal dominant (AD), and ALA dehydratase deficiency porphyria (ADP), which is autosomal recessive. ADP is exceptionally rare and will not be discussed further.³ VP and HCP can also cause photosensitivity, occurring either alone or during an acute neurovisceral attack.^{4–7}

As with many very rare conditions, AHPs present with heterogeneous and non-specific clinical features, meaning recognition of an initial acute porphyria attack, can be particularly difficult, thus diagnosis and implementation of specific, effective treatment may be delayed. Timely access to appropriate specialist tests and interpretative advice, essential in confirming and ruling out a diagnosis of AHP, is important for optimal care of patients with acute attacks and those with prior unexplained symptoms in whom the possibility of underlying AHP is being considered. Hospital management of the acute porphyria attack has however improved and there are promising new treatments for severely affected patients.⁸ More evidence is emerging of the burden of chronic symptoms, the impact of coincident health problems and long-term complications attributable to AHP.⁹ These factors are the focus of this update, as they influence the way in which patients should be managed by local clinical teams and specialist AHP services.

GENETICS AND EPIDEMIOLOGY

There is considerable genetic heterogeneity in AIP, VP and HCP with approximately 700 pathogenic variants described to date in the causative genes (table 1).¹⁰ Most pathogenic variants are unique to one kindred or limited to a few families. However, several founder mutations exist, the best known being hydroxymethylbilane synthase (HMBS) gene pTrp198X in more than 50% of AIP cases in Northern Sweden¹¹ and protoporphyrinogen



© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Schulenburg-Brand D, Stewart F, Stein P, et al. *J Clin Pathol* 2022;**75**:537–543.

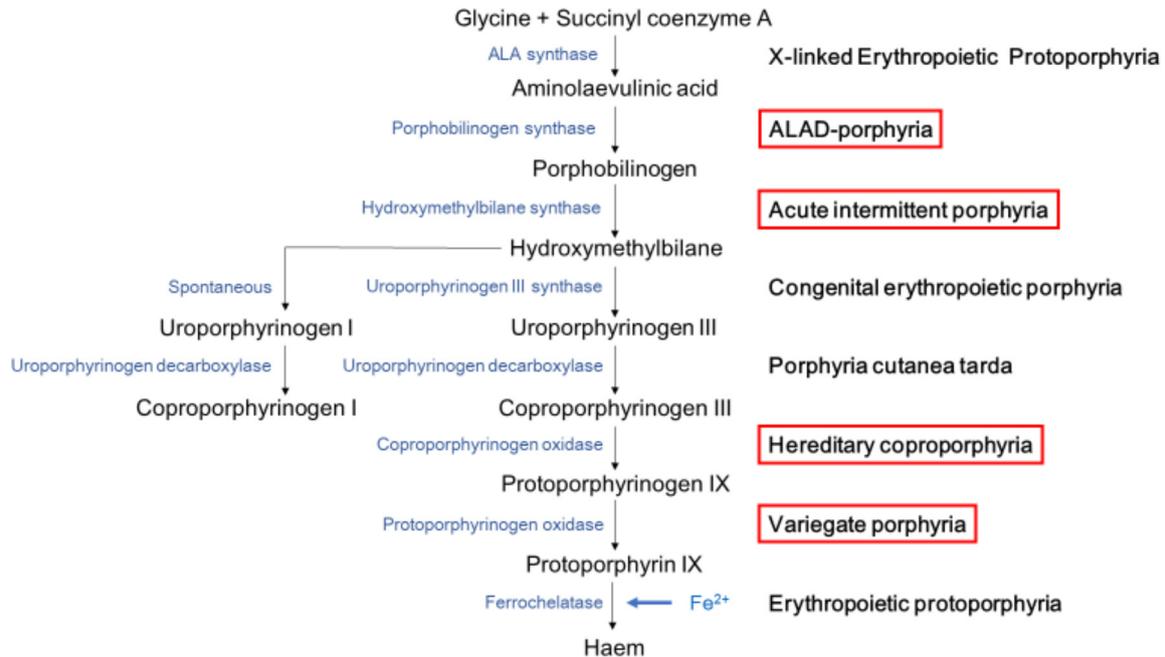


Figure 1 Haem biosynthetic pathway. Acute hepatic porphyrias are shown in text box. ALAD, 5-aminolaevulinic acid dehydratase.

oxidase gene pArg59Trp in over 95% of VP cases in South Africa.¹²

Estimates of incidence and prevalence of the AD AHPs vary because of low clinical penetrance and the lack of clear non-overlapping definitions to describe groups of patients with different clinical and biochemical presentations. For AIP, studies of samples from blood donors in France,¹³ confirmed by searching exome/genome databases,^{14,15} have identified *HMBS* pathogenic variants in approximately 1:1700 Caucasians. The prevalence of symptomatic AIP is estimated to be around 1:185 000 in Europe,¹⁶ which suggests a clinical penetrance in the general population of 0.5%–1%.^{14,16} However, a higher penetrance of 23% has been reported within affected families suggesting additional genetic and shared environmental factors are involved.¹⁵ Overall, however, the majority of those who inherit a pathogenic variant will remain asymptomatic throughout their life. The incidence of symptomatic VP is around half and symptomatic HCP an eighth of that of AIP (ratio 1.00:0.62:0.15) (table 1).¹⁶ The calculated prevalence of all symptomatic AHP was 10 per

million.¹⁶ In AIP, null mutations which completely abolish *HMBS* enzyme activity may also be linked with a more severe phenotype and increased clinical presentation.¹⁵

PATHOGENESIS AND PRECIPITATING FACTORS

Acute attacks are exceedingly rare before puberty and occur most commonly in young adults, with a preponderant incidence in females of reproductive age, some of whom experience recurrent attacks with a premenstrual pattern.

Acute attacks may be triggered by many drugs (prescribed or recreational),¹⁷ alcohol,¹⁸ fluctuating female sex hormones (particularly progesterone),¹⁹ caloric restriction (fasting, rapid weight loss),⁴ smoking, infection or other sources of ‘stress’.²⁰ However, attacks can occur without a clear precipitating event being identified. These factors upregulate hepatic *ALAS1* resulting in an increase in porphyrin precursors proximal to a deficient *HMBS*, the primary defect in AIP, but which is secondarily inhibited by accumulating porphyrinogens in VP and HCP

Table 1 Distinguishing features of the acute hepatic porphyrias

Type of porphyria	Enzyme deficiency	Gene	Incidence per million*	Clinical presentation	Increased haem pathway metabolites
ALA dehydratase porphyria	ALA dehydratase	<i>ALAD</i>	Exceptionally rare†	Acute attacks	Urine: ALA Red cell: zinc protoporphyrin
Acute intermittent porphyria	Hydroxymethylbilane synthase	<i>HMBS</i>	0.13	Acute attacks	Urine: ALA, PBG, uro Faeces: copro III:I ratio normal Plasma: FEP at 615–622 nm
Hereditary coproporphyria	Coproporphyrinogen oxidase	<i>CPOX</i>	0.02	Acute attacks and/or bullae and skin fragility	Urine: ALA, PBG, copro III Faeces: copro III:I ratio>1.5 Plasma: FEP at 615–622 nm
Variagate porphyria	Protoporphyrinogen oxidase	<i>PPOX</i>	0.08	Acute attacks and/or bullae and skin fragility	Urine: ALA, PBG, copro III Faeces: copro III:I ratio>1.5, proto>copro Plasma: FEP at 624–628 nm

*Symptomatic incidence in European population.¹⁶

†Only eight cases reported to date.³

ALA, aminolaevulinic acid; ALAD, 5-aminolaevulinic acid dehydratase; copro, coproporphyrin; FEP, fluorescence emission peak; PBG, porphobilinogen; proto, protoporphyrin; uro, uroporphyrin.

(figure 1).²¹ Many drugs and progesterone are potent inducers of ALAS1, whereas others increase haem requirements by inducing CYPs. Inflammation and infection result in increased haem catabolism by haem oxygenase, and caloric restriction induces ALAS1 activity by activating the peroxisome proliferator-activated receptor gamma-coactivator 1- α .²² The exact mechanism whereby excess ALA and/or PBG causes neurotoxicity is not fully understood,^{7 23} especially since some patients with AIP have persistently elevated excretion of ALA and PBG despite being asymptomatic.²⁴ The increased precursor release results in damage to the autonomic, peripheral and central nervous systems causing all of the characteristic clinical features described below.

CLINICAL FEATURES OF ACUTE NEUROVISCERAL ATTACKS

The clinical features of an acute attack of porphyria are non-specific. Pain, the predominant feature, is mainly abdominal, severe and typically lasts for several days,²⁰ although it may take longer to fully resolve. Pain in the lower back and upper legs is common.²⁵ Examination is usually unremarkable, and in particular the abdomen is usually soft and non-tender, but with reduced or absent bowel sounds.^{25 26}

Nausea and vomiting are very common, occurring in about 85% of cases,²⁶ with constipation present in about half.²⁵ Hypertension and tachycardia occur in about 60% of acute attacks, probably related to the effects of porphyrin precursors on the autonomic nervous system. Cardiac dysrhythmias occur in a small number of cases.²⁷

Some patients behave irrationally during acute attacks, with anxiety, paranoia and confusion. These features nearly always occur in the context of acute pain, and there is little evidence that porphyria is a cause of isolated psychiatric symptoms apart from generalised anxiety and depression.²⁸

During an acute attack, weakness and altered sensation are typically mild and improve as the pain resolves. However, in a small number of cases, severe, progressive peripheral neuropathy develops, which can be several weeks after the onset of abdominal pain, although this is variable. The neuropathy can worsen, even after the acute pain resolves, with a Guillain-Barré-like picture. Characteristically, proximal muscle weakness occurs in the upper limbs first²⁹ and can progress to involve the legs and cause respiratory failure. Cranial nerves can be involved, with the facial, vagus and hypoglossal nerves most often affected, which can cause swallowing difficulties. Sensory neuropathy is less common, but can cause numbness over the torso and thighs, with severe pain sometimes a feature. Cases gradually resolve with respiratory support, and some patients may need prolonged mechanical ventilation. After recovery, some degree of peripheral neuropathy can persist, with foot drop and wrist drop being fairly typical.³⁰ There are no specific clinical features or biomarkers which identify patients at risk of this complication.

Seizures occur in about 5%–10% of attacks^{20 31} and may be associated with hyponatraemia. Posterior reversible encephalopathy syndrome is a rare but well-described complication of acute attacks, usually associated with severe hypertension.^{30 32}

Hyponatraemia occurs in 30%–40% of attacks and is usually mild but can be severe ($\text{Na} < 125 \text{ mmol/L}$) in up to 5% of cases.²⁰ Hyponatraemia in acute attacks is multifactorial, vasopressin (antidiuretic hormone) being stimulated by pain, nausea and volume depletion due to vomiting and is potentially exacerbated by treatment with intravenous dextrose in water solutions and opioid analgesia. In combination with unexplained abdominal pain, it is perhaps the most distinctive indication that the pain is

due to acute porphyria, rather than other commoner causes. In severe attacks, sodium concentrations below 110 mmol/L may occur and are responsible for many of the severe complications, including acute confusional states and seizures.^{26 33}

During a severe attack, high urine concentrations of porphyrins cause red or dark coloured urine. On exposure to bright light, the urine may become reddish-purple over a few hours. This is not a constant feature and urine discolouration is a common observation in many acutely unwell patients without porphyria, possibly due to dehydration or hyperbilirubinaemia.

The incidence of death occurring as a complication of an attack of acute porphyria is not known, although it does appear to be very rare and decreasing.³⁴ Death can be caused by cardiac dysrhythmia, severe hyponatraemia and as a complication of treatment. Very rarely severe, progressive peripheral neuropathy causes respiratory failure and death over a period of months.

Long-term complications of AHPs

Chronic pain often occurs in patients with a history of recurrent acute attacks, as seen mostly in AIP. In the EXPLORE Study of severely affected AHP patients with three or more attacks in the preceding 12 months, 65% of patients reported chronic symptoms between attacks, including pain, mood and sleep disturbance, tiredness and gastrointestinal symptoms.⁹ The exact origin of these symptoms is unclear, but may be related to chronic neuropathy, biochemical abnormalities caused by porphyria, iatrogenic complications and stress associated with a chronic illness. Overall, patients experience considerable long-term burden of psychological illness as a consequence of the acute and chronic symptoms of the disease.

Chronic kidney disease (CKD) occurs commonly in symptomatic patients with acute porphyria, predominantly AIP. A 10-year cohort study of patients with AIP in France found that CKD (defined as estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73 m}^2$) was present in 59% of symptomatic patients, compared with 11% in asymptomatic carriers.³⁵ Hypertension was present in 62% of symptomatic patients and 2.7% developed end-stage renal disease. Most patients had tubulointerstitial nephropathy, probably caused by the toxic effects of porphyrin precursors.³⁵

Various studies have shown an increased risk of hepatocellular carcinoma (HCC) in patients with acute porphyria, with a Swedish study suggesting an incidence of 0.8% per year³⁶; similarly, 1.5% of patients with acute porphyria had HCC in a survey of patients in the USA.³⁷ HCC in acute porphyria is typically associated with normal alpha fetoprotein concentration and the absence of cirrhosis.^{36 37} Unlike other chronic complications, the increased risk does not seem to be associated with porphyria activity or symptoms, but does increase with age.

There is currently no international consensus on the most appropriate surveillance strategy to monitor long-term complications in AHPs. However, regular hepatic imaging and monitoring blood pressure and renal function after the age of 50 years should be considered.

DIAGNOSTIC APPROACH

Sample requirements and stability

Fresh spot urine samples should be collected into a plain container and protected from light while awaiting transport to the laboratory. Samples should be stored at 4°C in the dark when awaiting analysis or posting, which can be at room temperature. Priority post should be used with the aim of receipt within 24 hours as PBG has been shown to decrease by 20% after 2 days

at room temperature even when protected from light.³⁸ Urine, faecal and whole blood porphyrins are stable at room temperature for at least 2 days and ALA for 7 days.^{38 39} Urine PBG and porphyrins demonstrate a loss of 37%³⁹ and 50%,⁴⁰ respectively, when exposed to light for 24 hours. Separated plasma porphyrins are even more susceptible to light degradation with 50% loss after 6 hours.³⁹

Diagnosing an acute attack

Production and urinary excretion of the haem precursors PBG and ALA are always increased during an acute attack in AIP, VP and HCP.⁴ Diagnosis in a newly presenting patient therefore requires demonstration of a substantial increase in PBG excretion, usually greater than 10 times the upper reference limit,⁴¹ in a fresh, random urine sample. However, in patients with AIP, particularly those who have had previous attacks, PBG excretion can be persistently and significantly increased and interpretation in these patients requires knowledge of the patient's baseline excretion.⁴² In contrast, as symptoms resolve in VP and HCP, urine PBG excretion may return to normal within days and urine porphyrin analysis is required.³⁹ It is our practice to recommend that samples should be collected when patients are symptomatic. If urine PBG is normal and there is concern about a delay between the acute attack and the collection of the urine sample, then faecal and plasma porphyrins should be analysed, which additionally confirm abnormalities in urine porphyrins secondary to other illnesses.⁴³ International approaches differ with regards to the best diagnostic strategies and the European Porphyria Network has set up a task group to produce a best practice approach to diagnosis.

PBG is not increased in ADP, and urine ALA should therefore be measured if ADP is suspected,⁴ for example, in children, or if there is a suspicion of lead toxicity.⁴⁴

Quantitative urine PBG and porphyrin results should be expressed as a ratio to urine creatinine to account for urinary concentration. Very dilute urines (eg, urine creatinine < 2 mmol/L) as seen in children or patients on intravenous fluids may yield inaccurate results when concentrations are close to the detection

limits of the analytical methods and repeat samples should be requested.³⁹

The reliability and availability of screening tests for semiquantitative PBG is now very limited following the withdrawal of a commercially available assay (Trace PBG kit, Thermo Scientific). Many hospital laboratories no longer analyse urine PBG and rely on regional or national referral of samples. Urgent testing should be discussed with the laboratory prior to dispatch and results should be available within 24 hours of sample receipt in the testing laboratory in order for appropriate treatment to be initiated.³⁹

Diagnosing the type of AHP

Each of the acute porphyrias is characterised by a specific pattern of haem precursor and porphyrin accumulation and can be identified by testing urine, plasma and faeces⁴⁵ (table 1, figure 2). VP can be distinguished from the other acute porphyrias by the presence of a distinct plasma porphyrin fluorescence emission peak (FEP) at 624–628 nm. If there is no FEP, or a peak between 615 and 622 nm, then faecal porphyrin analysis is required to distinguish AIP from HCP. In HCP, faecal coproporphyrin III is greatly increased and the ratio of isomer III to isomer I is therefore abnormally increased.⁴⁵

Role of genetics

DNA analysis is normally performed to confirm the diagnosis of AHP and is useful to assist in family screening. Newly diagnosed patients are likely to have genetically affected, frequently latent relatives, and families should therefore be offered cascade testing so that those affected can be advised how to minimise their risk of acute attacks.⁴⁶ In a small number of patients pathogenic variants are not found, and family testing is dependent on metabolite measurement, which has significant limitations and should be managed with the support of a porphyria specialist.⁴⁶

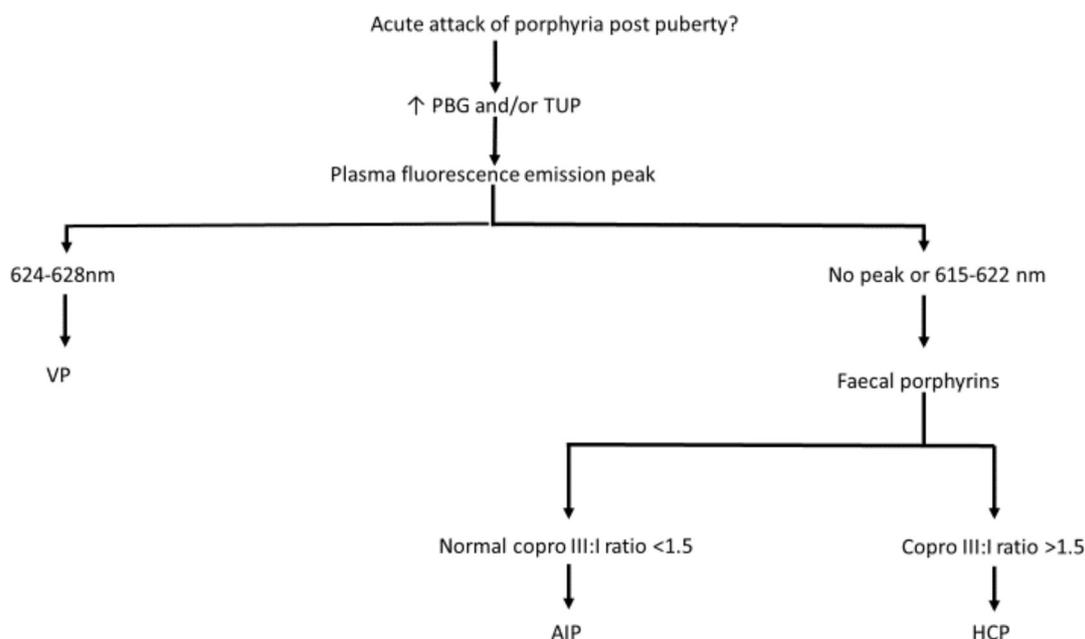


Figure 2 Laboratory diagnostic algorithm in patients with symptoms suggestive of AHP. AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; copro, coproporphyrin; HCP, hereditary coproporphyria; PBG, porphobilinogen; TUP, total urine porphyrins; VP, variegate porphyria.

Excluding a diagnosis of AHP in symptomatic patients or those with recent symptoms

There may be circumstances in which there is a delay in patients presenting for testing or when the possibility of acute porphyria is only considered after symptoms have resolved. In addition, patients with undiagnosed symptoms may research the internet which will lead some to request testing for acute porphyria. In this situation, we advise their clinician to send samples for urine PBG, faecal and plasma porphyrins to a specialist laboratory. After onset of active porphyria, there is good evidence that PBG excretion remains increased for months to years in AIP,⁴² and similarly that the characteristic plasma porphyrin FEP remains detectable in VP⁴⁷ and that in HCP the faecal coproporphyrin isomer ratio is abnormal in adults.⁴⁸ If all of these findings are normal, this makes acute porphyria as a cause of the previous illness extremely unlikely.

TREATING AN ACUTE ATTACK

Patients should usually be admitted to hospital for clinical evaluation, exclusion of other diagnoses, monitoring and treatment. Mild attacks can be managed symptomatically for up to 24 hours with regular review which should include pain score, neurological function and plasma sodium as well as standard clinical observations. Severe attacks should be treated with human haemin.^{25 49} Liaison with a porphyria specialist is advised, which in Great Britain would be with the National Acute Porphyria Service.

The objective of all treatments is to suppress the hepatic haem pathway by reducing activity of the rate limiting enzyme, ALAS1. This is achieved by supplementing hepatic haem stores with intravenous haemin or targeting ALAS1 mRNA for degradation through RNA interference. Carbohydrate loading similarly represses ALAS1 activity, although to a lesser extent.^{5 22 25}

Supportive treatment

Factors that may have triggered the attack should be removed, including stopping drugs that are not safe in porphyria and treating infection. Supportive and symptomatic treatments (eg, for nausea, constipation, hypertension) should be started as needed, ensuring all medication is checked for safety by consulting an authoritative database, for example, the UK Porphyria Medicines Information Service (<https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyrin/>) or the Norwegian-EPNET database (<http://www.drugs-porphyrin.org/>).^{50 51}

Most patients experience severe pain and require large amounts of opiate analgesia.²⁰ Opiates should be prescribed regularly (rather than as required) by oral or parenteral routes for the duration of the attack but stopped before the patient leaves hospital. Regular opiate use should be avoided in patients with chronic neuropathic pain that persists after the acute episode has resolved to avoid the risk of dependence and addiction. Gabapentinoids may be helpful in this situation. Input from a specialist pain team should be sought for patients with severe acute or chronic pain.

Intravenous fluid replacement must be managed carefully to minimise the risk of hyponatraemia, avoiding hypotonic dextrose solutions. If hyponatraemia is present, it should be assessed and treated in line with local guidelines and human haemin should be started as soon as possible. Correction of hyponatraemia should not exceed 8 mmol/L per 24 hours. Intensive care input should be sought if plasma sodium falls below 120 mmol/L or if the patient is symptomatic.

A high carbohydrate diet should be started if oral intake is tolerated. In patients with nausea or vomiting, carbohydrate can be provided as intravenous 5% dextrose in normal saline up to 2 L daily, but dextrose in water infusions is not recommended.

If peripheral neuropathy is present, human haemin should be started, in conjunction with advice from porphyria specialists. Patients with respiratory failure will usually require management on intensive care, and artificial ventilation may be needed for a period of several months. Regular intensive physiotherapy is important for recovery of function which typically takes 6–12 months.

Specific treatment

Human haemin is the treatment of choice for moderate or severe attacks, including any patient with complications (neuropathy, hyponatraemia, seizures, psychosis) or with severe symptoms. Human haemin should be given in the first few days of the attack to be most effective, although it may also be indicated if symptoms are persistent despite symptomatic treatment. In a patient without a previous diagnosis of AHP, it is important to confirm the attack by demonstrating increased urine PBG excretion before starting human haemin. In patients with known porphyria who are present with typical attack features, it may be reasonable to start haemin without waiting for a PBG result especially if the patient is very unwell.

Normosang (human haemin, Recordati Rare Diseases) is a concentrated solution containing 250 mg haem stabilised as a complex with arginine in each 10 mL vial. The recommended dose is 3 mg/kg body weight up to a maximum of 250 mg given on 4 consecutive days. The required volume of human haemin is mixed with 100 mL normal saline (or 100 mL 20% albumin) immediately before use and infused ideally through a central line, or a peripheral cannula inserted into a large vein, over 30–45 min. The vein must be flushed thoroughly with normal saline immediately after the haemin. Thrombophlebitis is a common side effect but can be avoided by infusing through a central line. Allergic reactions including anaphylaxis are extremely rare.

Intravenous carbohydrate loading (typically with 2 L of normal saline containing 10%–20% glucose given over 24 hours through a central line) is only indicated for minor attacks, or when human haemin is not available, and although rarely used in the UK is advised by experts elsewhere.^{25 49}

Treating recurrent attacks

Patients with recurrent attacks should be managed with advice from a porphyria specialist. Prophylactic human haemin is currently the most widely used treatment despite being an unlicensed use of the drug with a poor evidence base. Most patients have limited benefit from prophylactic haemin and continue to have hospital admissions with attacks and debilitating symptoms especially chronic pain.⁵² Side effects include difficulty maintaining central venous access which is a requirement for continued treatment, hepatic iron overload with inflammatory changes and loss of efficacy over time.

Gonadorelin analogues provide at least partial benefit in about 50% of females with recurrent premenstrual attacks, but severe oestrogen deficiency side effects make this treatment unacceptable for the majority of patients.⁵³ Where used, the treatment should be initiated during or soon after menses in order to reduce the risk of inducing an attack. A suggested treatment protocol has been published elsewhere.⁵³

Givosiran (Givlaari, Alnylam Pharmaceuticals) is a newly developed small interfering RNA therapy which targets hepatic ALAS1 RNA for degradation and is administered as a 2.5 mg/kg monthly subcutaneous injection. Placebo-controlled clinical trials have shown encouraging results in patients with recurrent attacks, with givosiran showing high and sustained efficacy in preventing attacks although there are limited data on use in VP and HCP.⁸ There are few serious side effects but close monitoring of renal and liver function is required.

Liver transplantation is a treatment when other options have failed and results in biochemical and clinical remission, but cannot reverse previous long-term damage as a consequence of severe recurrent attacks.⁵⁴

SPECIFIC PATIENT GROUPS AND AREAS OF RISK

Pregnancy

Pregnant women with acute porphyria have a higher risk of attacks because of the hormonal changes associated with pregnancy, although most have completely normal pregnancies.^{55 56} Drugs such as ergometrine that are unsafe in porphyria should be avoided, except in life-threatening situations. Good analgesia should be provided during labour and prolonged fasting should be avoided. Regional or general anaesthesia are safe provided porphyria drug restrictions are adhered to. Attacks during pregnancy or in breastfeeding mothers should be treated with human haemin in the usual way and there is no evidence of adverse effects on mother or child, although the drug is not licensed for use in pregnancy.

Infertility treatment

Women with acute porphyria who wish to undertake in vitro fertilisation (IVF) should be counselled about the increased risk of attacks associated with hormonal treatments.⁵⁷ The treating medical team should liaise frequently with a porphyria specialist to choose appropriate drugs and doses balancing benefit with the risk of attacks in each patient. Biochemical monitoring of urine PBG may be useful to establish a pretreatment baseline, to provide early warning of impending attacks and to differentiate attacks from other causes of pain such as ovarian hyperstimulation syndrome.

Bariatric surgery

Bariatric surgery is a high-risk procedure in patients with acute porphyria as the sudden, extreme weight loss carries a significant risk of triggering acute attacks.⁵⁸ Reversible procedures are

recommended and close liaison with a dietician and a porphyria specialist is essential.

Chemotherapy

Patients with acute porphyria who require chemotherapy should be under the care of a porphyria specialist. Porphyria drug safety restrictions are relevant for symptomatic and supportive treatment (eg, for nausea), but choice of chemotherapy drugs should be optimised for the cancer. No drug should be restricted on the basis that it might cause a porphyria attack if it is life-saving or likely to be of major clinical benefit.

Handling editor Patrick J Twomey.

Contributors DS-B: concept and design, coauthored Diagnostic approach section, authored tables and graphs and take-home messages and edited drafts. FS: authored Introduction, Genetics and epidemiology and Pathogenesis and precipitating factors sections and edited drafts. DR: authored Clinical features of acute neurovisceral attacks and Long-term complications of AHPs sections. PS: authored Treating an acute attack and Specific patient groups and areas of risk sections. MB: authored Abstract and coauthored the Diagnostic approach sections and edited the drafts. All authors were involved in reviewing the drafts and DS-B, MB and FS prepared responses for referees.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD

Danja Schulenburg-Brand <http://orcid.org/0000-0002-2494-428X>

REFERENCES

- 1 Karim Z, Lyoumi S, Nicolas G, *et al*. Porphyrias: a 2015 update. *Clin Res Hepatol Gastroenterol* 2015;39:412–25.
- 2 Phillips JD. Heme biosynthesis and the porphyrias. *Mol Genet Metab* 2019;128:164–77.
- 3 Lahiji AP, Anderson KE, Chan A, *et al*. 5-Aminolevulinic acid dehydratase porphyria: update on hepatic 5-aminolevulinic acid synthase induction and long-term response to hemin. *Mol Genet Metab* 2020;131:418–23.
- 4 Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. *Br J Haematol* 2017;176:527–38.
- 5 Anderson KE. Acute hepatic porphyrias: Current diagnosis & management. *Mol Genet Metab* 2019;128:219–27.
- 6 Wang B, Rudnick S, Cengia B, *et al*. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun* 2019;3:193–206.
- 7 Bonkovsky HL, Dixon N, Rudnick S. Pathogenesis and clinical features of the acute hepatic porphyrias (AHPs). *Mol Genet Metab* 2019;128:213–8.
- 8 Balwani M, Sardh E, Ventura P, *et al*. Phase 3 trial of RNAi therapeutic Givosiran for acute intermittent porphyria. *N Engl J Med* 2020;382:2289–301.
- 9 Gouya L, Ventura P, Balwani M, *et al*. Explore: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology* 2020;71:1546–58.
- 10 Yasuda M, Chen B, Desnick RJ. Recent advances on porphyria genetics: Inheritance, penetrance & molecular heterogeneity, including new modifying/causative genes. *Mol Genet Metab* 2019;128:320–31.
- 11 Lee JS, Anvret M. Identification of the most common mutation within the porphobilinogen deaminase gene in Swedish patients with acute intermittent porphyria. *Proc Natl Acad Sci U S A* 1991;88:10912–5.
- 12 Meissner PN, Dailey TA, Hift RJ, *et al*. A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. *Nat Genet* 1996;13:95–7.
- 13 Nordmann Y, Puy H, Da Silva V, *et al*. Acute intermittent porphyria: prevalence of mutations in the porphobilinogen deaminase gene in blood donors in France. *J Intern Med* 1997;242:213–7.
- 14 Chen B, Solis-Villa C, Hakenberg J, *et al*. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. *Hum Mutat* 2016;37:1215–22.
- 15 Lenglet H, Schmitt C, Grange T, *et al*. From a dominant to an oligogenic model of inheritance with environmental modifiers in acute intermittent porphyria. *Hum Mol Genet* 2018;27:1164–73.

Take home messages

- ⇒ A diagnosis of acute hepatic porphyria (AHP) should be considered in any patient, especially young females, with repeated presentations of unexplained non-localising severe abdominal pain, especially if associated with hyponatraemia.
- ⇒ A urine porphobilinogen, collected during the acute illness, is needed to biochemically confirm an acute attack of porphyria in a newly presenting patient.
- ⇒ Removing any precipitating factors, treating symptoms and administration of human haemin for severe or complicated acute attacks are the mainstay of treatment.
- ⇒ Care for patients with active AHP should be shared with a porphyria specialist; in the UK, this service is provided by the National Acute Porphyria Service.

- 16 Elder G, Harper P, Badminton M, *et al.* The incidence of inherited porphyrias in Europe. *J Inherit Metab Dis* 2013;36:849–57.
- 17 Hift RJ, Thunell S, Brun A. Drugs in porphyria: from observation to a modern algorithm-based system for the prediction of porphyrogenicity. *Pharmacol Ther* 2011;132:158–69.
- 18 Doss MO, Kühnel A, Gross U. Alcohol and porphyrin metabolism. *Alcohol Alcohol* 2000;35:109–25.
- 19 Anderson KE, Bradlow HL, Sassa S, *et al.* Studies in porphyria. *Am J Med* 1979;66:644–50.
- 20 Hift RJ, Meissner PN. An analysis of 112 acute porphyric attacks in Cape town, South Africa. *Medicine* 2005;84:48–60.
- 21 Meissner P, Adams P, Kirsch R. Allosteric inhibition of human lymphoblast and purified porphobilinogen deaminase by protoporphyrinogen and coproporphyrinogen. A possible mechanism for the acute attack of variegate porphyria. *J Clin Invest* 1993;91:1436–44.
- 22 Handschin C, Lin J, Rhee J, *et al.* Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. *Cell* 2005;122:505–15.
- 23 Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. *Semin Liver Dis* 1998;18:43–52.
- 24 Floderus Y, Sardh E, Möller C, *et al.* Variations in porphobilinogen and 5-aminolevulinic acid concentrations in plasma and urine from asymptomatic carriers of the acute intermittent porphyria gene with increased porphyrin precursor excretion. *Clin Chem* 2006;52:701–7.
- 25 Anderson KE, Bloomer JR, Bonkovsky HL, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005;142:439–50.
- 26 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004–8.
- 27 Dhoble A, Patel MB, Abdelmoneim SS, *et al.* Relation of porphyria to atrial fibrillation. *Am J Cardiol* 2009;104:373–6.
- 28 Millward LM, Kelly P, King A, *et al.* Anxiety and depression in the acute porphyrias. *J Inherit Metab Dis* 2005;28:1099–107.
- 29 Puy H, Gouya L, Deybach J-C. Porphyrias. *Lancet* 2010;375:924–37.
- 30 Gandhi Mehta RK, Caress JB, Rudnick SR, *et al.* Porphyric neuropathy. *Muscle Nerve* 2021;64:140–52.
- 31 Bonkovsky HL, Maddukuri VC, Yazici C, *et al.* Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. *Am J Med* 2014;127:1233–41.
- 32 Jaramillo-Calle DA, Solano JM, Rabinstein AA, *et al.* Porphyria-induced posterior reversible encephalopathy syndrome and central nervous system dysfunction. *Mol Genet Metab* 2019;128:242–53.
- 33 Solares I, Tejedor M, Jericó D, *et al.* Management of hyponatremia associated with acute porphyria-proposal for the use of tolvaptan. *Ann Transl Med* 2020;8:1098–116.
- 34 Fraunberg MvonUZ, Pischik E, Udd L, *et al.* Clinical and biochemical characteristics and genotype-phenotype correlation in 143 Finnish and Russian patients with acute intermittent porphyria. *Medicine* 2005;84:35–47.
- 35 Pallet N, Mami I, Schmitt C, *et al.* High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. *Kidney Int* 2015;88:386–95.
- 36 Innala E, Andersson C. Screening for hepatocellular carcinoma in acute intermittent porphyria: a 15-year follow-up in northern Sweden. *J Intern Med* 2011;269:538–45.
- 37 Saberi B, Naik H, Overbey JR, *et al.* Hepatocellular carcinoma in acute hepatic porphyrias: results from the longitudinal study of the U.S. porphyrias Consortium. *Hepatology* 2021;73:1736–46.
- 38 Blø AR, Dahlberg IMU, Sandberg S. Stability of ALA and PBG in urine samples stored at room temperature. International Congress on porphyrins and porphyrias. *Milan* 2019.
- 39 Woolf J, Marsden JT, Degg T, *et al.* Best practice guidelines on first-line laboratory testing for porphyria. *Ann Clin Biochem* 2017;54:188–98.
- 40 Badminton MN, Whatley SD, Sardh E. Porphyrins and the porphyrias. In: Rifai N, Horvath AR, Witter CT, eds. *Tietz textbook of clinical chemistry and molecular diagnostics*. 6th edn. St Louis: Elsevier, 2017: 776–99.
- 41 Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepatol* 2015;3:17–26.
- 42 Marsden JT, Rees DC. Urinary excretion of porphyrins, porphobilinogen and δ -aminolaevulinic acid following an attack of acute intermittent porphyria. *J Clin Pathol* 2014;67:60–5.
- 43 Hift RJ, Meissner PN. Miscellaneous abnormalities in porphyrin production and disposal. In: Kadish K, Smith K, Guillard R, eds. *Medical aspects of porphyria*. Amsterdam: Academic Press, 2003: 151–67.
- 44 Mitra P, Sharma S, Purohit P, *et al.* Clinical and molecular aspects of lead toxicity: an update. *Crit Rev Clin Lab Sci* 2017;54:506–28.
- 45 Whatley SD, Mason NG, Woolf JR, *et al.* Diagnostic strategies for autosomal dominant acute porphyrias: retrospective analysis of 467 unrelated patients referred for mutational analysis of the HMBS, CPOX, or PPOX gene. *Clin Chem* 2009;55:1406–14.
- 46 Whatley SD, Badminton MN. Role of genetic testing in the management of patients with inherited porphyria and their families. *Ann Clin Biochem* 2013;50:204–16.
- 47 Hift RJ, Davidson BP, van der Hooft C, *et al.* Plasma fluorescence scanning and fecal porphyrin analysis for the diagnosis of variegate porphyria: precise determination of sensitivity and specificity with detection of protoporphyrinogen oxidase mutations as a reference standard. *Clin Chem* 2004;50:915–23.
- 48 Allen KR, Whatley SD, Degg TJ, *et al.* Hereditary coproporphyria: comparison of molecular and biochemical investigations in a large family. *J Inherit Metab Dis* 2005;28:779–85.
- 49 Stein P, Badminton M, Barth J, *et al.* Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Ann Clin Biochem* 2013;50:217–23.
- 50 UK porphyria medicines information service. Provided by the Welsh medicines information centre, 2021. Porphyria safe drug list. Available: <https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria/> [Accessed 07 Oct 2021].
- 51 The drug database for acute porphyria. Available: <http://www.drugs-porphyria.org> [Accessed 03 Dec 2021].
- 52 Marsden JT, Guppy S, Stein P, *et al.* Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep* 2015;22:57–65.
- 53 Schulenburg-Brand D, Gardiner T, Guppy S, *et al.* An audit of the use of gonadorelin analogues to prevent recurrent acute symptoms in patients with acute porphyria in the United Kingdom. *JIMD Rep* 2017;36:99–107.
- 54 Lissing M, Nowak G, Adam R. European liver and intestine transplant association. liver transplantation for acute intermittent porphyria. *Liver Transpl* 2021;27:491–501.
- 55 Marsden JT, Rees DC. A retrospective analysis of outcome of pregnancy in patients with acute porphyria. *J Inherit Metab Dis* 2010;33:591–6.
- 56 Vassiliou D, Sardh E. Acute hepatic porphyria and maternal health: clinical and biochemical follow-up of 44 pregnancies. *J Intern Med* 2022;291:1–14.
- 57 Vassiliou D, Lindén Hirschberg A, Sardh E. Treatment with assisted reproduction technologies in women with acute hepatic porphyria. *Acta Obstet Gynecol Scand* 2021;100:1712–21.
- 58 Bonkovsky HL, Siao P, Roig Z, *et al.* Case records of the Massachusetts General Hospital. Case 20-2008. A 57-year-old woman with abdominal pain and weakness after gastric bypass surgery. *N Engl J Med* 2008;358:2813–25.