Porphyrias: implications for anaesthesia, critical care, and pain medicine

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Helen Findley BMBS BMed Sci FRCA
Anu Philips MBBS FRCA
Duncan Cole PhD MRCP FRCPath
Amanda Nair BM FRCA

Key points

- The acute porphyrias are acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolaevulinic acid dehydratase deficiency.
- Only the acute porphyrias deteriorate into acute neurovisceral crises.
- Fasting, dehydration, infection, and administration of many drugs can trigger acute crises; therefore, the safety of drugs should be checked against current databases.
- Diagnosis of acute neurovisceral crisis requires a high index of suspicion coupled with analysis of urine for porphobilinogen.
- Acute crises may be life threatening but can be aborted by early administration of haem arginate; management is otherwise supportive.

Helen Findley BMBS BMed Sci FRCA
Speciality Registrar in Anaesthesia
Sheffield Teaching Hospitals NHS Trust
Sheffield, UK

Anu Philips MBBS FRCA
Specialist Registrar in Anaesthesia
Sheffield Teaching Hospitals NHS Trust
Sheffield, UK

Duncan Cole PhD MRCP FRCPath
Clinical Senior Lecturer in Medical Biochemistry and Metabolic Medicine
Department of Infection, Immunity and Biochemistry, Cardiff University
Heath Park, Cardiff CF14 4XW, UK

Amanda Nair BM FRCA
Consultant Anaesthetist
Sheffield Teaching Hospitals NHS Trust
Northern General Hospital
Herries Road, Sheffield S5 7AU, UK
Tel: +44 114 2714818
Fax: +44 114 2269342
E-mail: amanda.nair@sth.nhs.uk
(for correspondence)

Definition

The porphyrias are a heterogeneous group of inherited disorders of haem biosynthesis. The name porphyria is derived from the Greek word for purple, 'porphyros'. This was the name given to the purple compound formed when blood was treated with concentrated sulphuric acid;[1] the disease was probably named porphyria due to the red discolouration of urine in affected patients.

Multiple classification systems exist; the most relevant to anaesthetists is acute and non-acute (Table 1). All acute porphyrias have the potential to develop acute neurovisceral crises. Precipitating factors are commonly encountered in the perioperative period; therefore, anaesthetists must be aware of the triggers and the management of an acute crisis. Non-acute porphyrias do not deteriorate into acute crises, are less relevant for anaesthetists, and will not be mentioned further in this article.

Pathogenesis

Porphyrins are organic cyclical compounds found in many aspects of biological life; the most important in humans is haem, the iron-containing ring structure found in haemoglobin, myoglobin, and all of the cytochromes.[2]

The haem biosynthetic pathway is most active in the liver and bone marrow. In the porphyrias, genetic defects cause deficiency of intermediary enzymes in this pathway (Fig. 1).

All acute porphyrias have the potential to develop acute neurovisceral crises when a precipitating event occurs (Table 2). Precipitating factors increase the demand for haem in the liver, for example, by inducing the haem-containing cytochrome P450 family of enzymes, which results in an increased flux through the pathway and accumulation of substrate before the enzyme defect. All enzyme defects seen in the acute porphyrias result in the accumulation of 5-aminolaevulinic acid (ALA). In acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP), porphobilinogen (PBG) is also elevated and levels are used to diagnose acute crises.

The symptoms and signs of acute neurovisceral crises are thought to result from neurological dysfunction in motor, sensory, and autonomic fibres and the central nervous system. The precise cause of neurological dysfunction remains a matter of debate. There are two main theories: the most widely held states that ALA is neurotoxic; the other proposes that haem deficiency is responsible for neurological dysfunction.

Inheritance

The gene mutations causing AIP, VP, and HCP are all inherited in an autosomal-dominant manner, with variable expression.[3] In all three conditions, there is a reduction in specific intermediary enzyme activity to ~50% of normal; however, 80% of carriers of the gene mutation will never manifest symptoms.[4] ALA dehydratase deficiency is inherited as an autosomal recessive condition.

Epidemiology

The overall prevalence of acute porphyrias in European countries is 1–2 in 100 000,[3] with AIP being the most common. In the UK, the incidence of newly diagnosed AIP is 0.16 per million per year,[5] equating to ~10 new cases per year in the UK.

The prevalence of the different acute porphyrias also varies geographically. Owing to the founder effect, AIP is more common in

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Table 1 Classification of porphyrias: acute and non-acute

Acute porphyrias	Non-acute porphyrias
AIP	Porphyria cutanea tarda
VP	Congenital erythropoietic porphyria
HCP	Erythropoietic protoporphyria
ALA dehydratase deficiency	

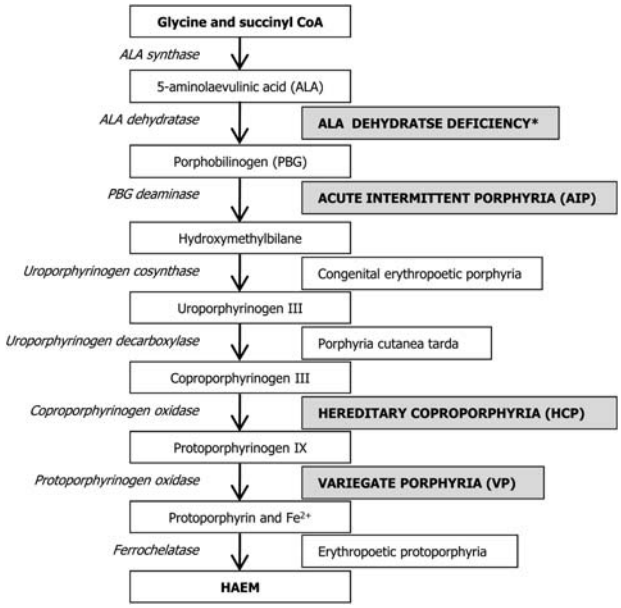

Fig 1 Haem biosynthetic pathway and the enzyme defects involved in different porphyrias. *Acute porphyrias are shown in bold.

Table 2 Triggers for acute crisis

General triggers for acute neurovisceral crisis	
Fasting	Endogenous hormones
Dehydration	Stress: physical/emotional
Infection	Smoking
Drugs	Alcohol

northern Sweden, affecting up to 1 per 1500.[3] VP is about half as common as AIP in Europe[6] but more widespread in the Afrikaner community in South Africa, where it is found in 1 per 250–500.[3] ALA dehydratase deficiency is extremely rare, with <10 cases reported since 1979.[3]

Implications of the acute porphyrias

The acute porphyrias have significant implications due to their propensity to develop potentially life-threatening neurovisceral crises, which can be triggered by a number of factors including drugs (Table 2). Non-acute porphyrias are less concerning for the anaesthetist as these patients do not develop acute crises.

Table 3 Presentation of acute crisis: symptoms and signs

Symptoms and signs (in order of incidence)	Features	May be misdiagnosed as
Abdominal pain	Recurrent, severe, poorly localized	Another cause of acute abdomen
	Associated nausea and vomiting	Endometriosis/pelvic inflammatory disease
	Absence of fever or leucocytosis	Irritable bowel syndrome
		Opiate addiction
Cardiovascular signs	Tachycardia	
	Tachyarrhythmia	
	Hypertension	
Weakness	Proximal>distal	Guillan–Barre syndrome
	Upper limbs>lower	Poliomyelitis
	Up to 20% develop respiratory failure[4]	Acute lead poisoning
	May progress to bulbar paresis in severe cases	Vasculitis
Psychiatric features	Mood disturbance	Anxiety disorder
	Confusion	Somatization disorder
	Psychosis	Acute psychosis
		Acute confusional state
Pain and sensory disturbance	Back, thigh, or extremity pain	Chronic fatigue syndrome
	Sensory neuropathy over the trunk	Fibromyalgia
		Chronic pain syndromes
Seizures	CNS manifestation of porphyria	Epilepsy
	Secondary to hyponatraemia (see below)	
Other autonomic features	Constipation	
	Gastroparesis	
	Postural hypotension	
Cutaneous lesions	Only in VP and HCP	Porphyria cutanea tarda
	Vesicular rash	Bullous skin disease
	Photosensitivity	
Hyponatraemia and other electrolyte disturbance	Low serum sodium	Other disorders of sodium and water balance
	Low serum magnesium	

Anaesthetists may be involved in the care of patients with diagnoses of porphyria in a number of settings:

- during acute crisis;
- during incidental surgery;
- for acute or chronic pain management.

Presentation of an acute crisis

The most common symptoms and signs of acute crisis are shown in Table 3. Almost all patients have severe abdominal pain, usually associated with a tachycardia. Neurological or psychiatric symptoms rarely occur in isolation. Skin lesions may be present during acute crises in patients with VP and HCP. Other clues to the diagnosis include urine that darkens on standing, hyponatraemia, or recent ingestion of trigger drugs (typically anticonvulsants, oral contraceptive pill, alcohol, or illicit drugs).

Crises are four to five times more common in women and usually occur in their early 30s.[7] A family history of porphyria may not be present, due to previously undiagnosed disease in asymptomatic carriers.

Acute crises may vary from a single attack that aborts quickly to those that go on to have frequent life-threatening attacks with multisystem involvement, respiratory, and bulbar paresis. Less than 10% develop recurrent attacks.[6] Symptoms and signs of acute crises also vary greatly and therefore can mimic other conditions. Patients having acute crises are frequently misdiagnosed, leading to inappropriate or delayed treatment. Acute porphyria should be excluded in any case of unexplained severe abdominal pain, especially if associated with tachycardia and neurological symptoms.

Implications for critical care

Patients presenting with an acute crisis to critical care may not have an established diagnosis or may have been misdiagnosed with another condition. Critical care admission may be required for supportive treatment, including respiratory support, control of seizures, or treatment of a precipitating infection.

Diagnostic tests in acute porphyria

The key to making the diagnosis lies in having a high index of suspicion in patients presenting with abdominal pain. Acute porphyria can be effectively ruled out by checking PBG levels in a fresh urine sample. Urine must be collected in a universal container and protected from light, as PBG will degrade rapidly when exposed to light,[8] increasing the likelihood of a false-negative result. All hospitals should have access to at least a semi-quantitative assay 24 h a day. Increased urine PBG levels confirm acute porphyria; levels are usually 10 times normal within a week of onset of an acute crisis.[3] A normal urine PBG level rules out AIP, VP, and HCP (but not ALA dehydratase deficiency) as a cause of current symptoms, but PBG may be mildly elevated in latent AIP or AIP in remission. Acute porphyria due to the rare condition of ALA dehydratase deficiency will not test positive for urine PBG; therefore, specialist advice is warranted if porphyria is strongly suspected in a patient with negative urine PBG. Cerebrospinal fluid samples in porphyria are usually normal.[6]

A positive result should be discussed with the appropriate regional specialist centre, where further investigations are coordinated. The original positive sample should be sent to the specialist centre[8] and a second, confirmatory sample may be useful, but is not critical, and treatment should not be delayed while waiting for this.

EDTA blood 5–10 ml should also be collected, and a small faecal sample, both protected from light. These samples are less urgent, but should preferably be obtained when the patient is unwell; they are used for biochemical analysis to determine the type of acute porphyria. Once the type of porphyria has been determined, DNA studies can identify the genetic mutation responsible. Family members can then be offered genetic counselling and screening.

Management of an acute crisis

Once the diagnosis of an acute crisis has been made, management consists of removing potential precipitants, giving i.v. haem arginate, and supportive measures.

Removing potential precipitants

All drugs being administered should be reviewed, with reference to a regularly updated safe drug list. However, in a life-threatening situation, emergency drugs should not be withheld due to concerns over their safety in porphyria; the acute porphyric attack can be treated if it occurs. Any intercurrent illness should be treated with the usual measures. Infection must be treated aggressively and should be actively excluded by septic screen if no other obvious trigger is found. Paracetamol is safe as an antipyretic and analgesic.[9]

Fasting will trigger continued production of porphyrins, so a catabolic state should be avoided by ensuring that the patient takes 200 g of glucose per day[6,9] by either administering carbohydrate energy supplements orally or via a nasogastric tube (e.g. 25% MAXIJUL, available from Nutricia) or through i.v. infusion. If the latter is used, we recommend the pharmacy to prepare 0.9% saline with 10% dextrose added (2 litres provide 200 g of glucose in 24 h),[9] as these patients are prone to hyponatraemia. Carbohydrate loading is also known to suppress hepatic ALA synthase activity and has been used to abort mild attacks.[4]

I.V. haem arginate

I.V. haem arginate therapy should be started as soon as possible, as it is associated with improved outcomes, including shorter hospital stay.[4] Haem arginate aims to suppress hepatic production of ALA and other porphyrin precursors by replenishing haem. The recommended dose of haem arginate is 3 mg kg^{-1} (to a maximum of 250 mg) once daily for 4 consecutive days and the course should be given in full.[9] Clinical improvement is usually rapid if treatment is started early in the course of an acute crisis; however, if treatment is delayed and extensive neuronal damage has occurred, the patient will be slow to recover. Treatment for longer than 4 days can be considered in these cases; however, there is no evidence for an improved outcome with longer courses of treatment.[4]

Haem arginate should be administered as an i.v. infusion over 30 min into a large vein or via a central line[9] and should be thoroughly flushed with saline on completion of the dose. Haem arginate is irritant to veins and may cause thrombophlebitis; this may lead to the loss of superficial veins and the consequent need for a central line. Haem arginate should be diluted in 100 ml of 0.9% sodium chloride in a glass bottle; however, a pragmatic but unlicensed approach, to avoid delaying emergency treatment, would be to use plastic containers or to administer in 100 ml of 20%

human albumin, ensuring preparation occurs immediately before administration.[9]

Supportive measures

Acute crisis is commonly associated with abdominal pain, but can be associated with back pain or pain in the limbs. Pain can be very severe and may require substantial doses of opioids. Nausea and vomiting are treated safely with prochlorperazine or ondansetron.[9] Lorazepam and midazolam in low doses are safe for anxiety; insomnia can be treated with zopiclone.[9] Haloperidol is safe and may be helpful in treating delirium. β-adrenergic blocking agents may be useful to control tachycardia and hypertension; glyceryl trinitrate can also be used safely.[9] Controlled correction of hyponatraemia may prevent seizures. Seizures can be safely terminated with boluses of benzodiazepines; however, prophylaxis can be difficult as many commonly used anticonvulsant drugs exacerbate acute porphyria. Levetiracetam, clonazepam, gabapentin, and vigabatrin are safe to use and magnesium sulphate may be used as an anticonvulsant.[6,9]

Ventilatory support is indicated if respiratory failure occurs. Evidence of functional impairment, for example, inability to cough or expectorate, are pragmatic markers of referral for critical care opinion. The role of non-invasive ventilation is questionable; patients with respiratory failure may also have bulbar weakness and gastric paresis, leading to a significant risk of aspiration of gastric contents. For these reasons, any patient with significant neurological deterioration should also be monitored closely.

Sedation is safe using propofol and alfentanil infusions.[9] The clinical safety of prolonged midazolam infusion is unknown.[9] Clonidine is not thought to be porphyrogenic within the normal therapeutic range; there is a case report of its use during acute crisis.[10]

Thromboembolic prophylaxis can be safely provided with any of the low-molecular-weight heparins and stress ulcer prevention using i.v. omeprazole or ranitidine is safe.[9]

Prognosis

A study in the USA, published in 1996, showed a mortality of 14% in patients admitted to hospital with an acute crisis. Nearly all the patients who died had advanced porphyria and required mechanical ventilation.[4] However, more recent studies have suggested that acute crises are rarely fatal.[6] Acute porphyria, whether symptomatic or not, carries an increased risk of hypertension, hepatocellular carcinoma, and chronic renal failure.[6]

1. Have a high index of suspicion in patients with unexplained abdominal pain
2. Send urine, protected from light, for PBG assay
3. Remove or treat triggering factors
4. Give i.v. haem arginate 3 mg kg^{-1} daily for 4 days
5. Avoid a catabolic state
6. May require large doses of morphine to control pain
7. Antiemetics—prochlorperazine and ondansetron are safe
8. Control tachycardia and hypertension with β-blocking agents
9. Seizures may be avoided by correcting hyponatraemia and treating with gabapentin, vigabatrin, or levetiracetam
10. Sedation with propofol and alfentanil is safe

Fig 2 Key principles of investigation and management of acute porphyrias.

Implications for anaesthesia

General principles

Any patient with suspected or confirmed acute porphyria undergoing surgery requires a full medical history, including detailed family history, and a thorough physical examination, along with careful neurological assessment. Particular attention should be given to the presence of peripheral neuropathy and autonomic instability, as they will influence the anaesthetic technique and also indicate active disease, with increased risk of acute crisis. However, most patients will have a negative family history and no clinical evidence of disease.

Acute porphyrias can be triggered by a number of factors present in the perioperative period (Table 2). Safe anaesthetic management of these patients requires knowledge of the type of porphyria and susceptibility to an acute crisis, awareness of the clinical features of an attack, and knowledge of safe pharmacological intervention.

All team members involved in the perioperative period should be informed of the patient's condition and implications of the disease. The patient can be admitted on the day of surgery, providing a thorough preoperative assessment has taken place. Ideally, preoperative assessment should be done by a senior anaesthetist involved in the case, as this may allay anxiety and aid in setting up a rapport. Anxiolysis with benzodiazepines or phenothiazines is recommended. Fasting periods should be minimized, but remain in accordance with local protocols, and i.v. dextrose saline infusion should be given to avoid calorie restriction.

Patients should be monitored after operation for symptoms and signs of an acute crisis, and are therefore not suitable for day-case surgery. Monitoring of urine PBG levels is not necessary routinely, although may be useful as an early marker of acute crisis in those patients who have recurrent acute attacks. In the event of an acute crisis, treatment is as advised in the previous section.

Regional anaesthesia

There is no absolute contradiction to the use of regional anaesthesia in porphyria. However, a thorough neurological and cardiovascular examination must be carried out by a senior clinician before a regional technique is undertaken, to diagnose pre-existing neurological deficits, and the presence of autonomic neuropathy. Untreated hypovolaemia and autonomic instability in the presence of central neuroaxial block may precipitate severe cardiovascular instability.

There have been various reports of regional anaesthesia being used successfully in patients with porphyria and we conclude that there is no evidence that a general anaesthetic is safer than a regional anaesthetic.

Table 4 Safety profile of commonly used drugs in anaesthesia.[10] Adapted from http://www.drugs-porphyria.org according to their classification. The safe drugs are not porphyrinogenic, possibly not porphyrinogenic or probably not porphyrinogenic. The unsafe drugs are porphyrinogenic or possibly porphyrinogenic. Unclassified drugs are shown in the undetermined column

Class of drug	Safe	Unsafe	Undetermined
Intravenous anaesthetic agents	Propofol	Thiopentone Ketamine	Etomidate
Inhalational anaesthetic agents	Isoflurane Desflurane Nitrous oxide	Sevoflurane	
Local Anaesthetics	Bupivicaine Prilocaine Lignocaine		Levobupivicaine Ropivicaine
Neuromuscular Blocking Agents and Reversal	Succinylcholine All non depolarising muscle relaxants Neostigmine		
Analgesics	Fentanyl Alfentanil Remifentanil Morphine Hydromorphone Meperidine Tramadol Ibuprofen Aspirin Diamorphine	Oxycodone Diclofenac	Pentazocine Mefenamic acid
Sedative premedication	Lorazepam Phenothiazines (Chlorpromazine) Temazepam		
Antibiotics	Gentamicin Co-amoxiclav Penicillins Vancomycin Tazocin Meropenem	Rifampicin Erythromycin	
Cardiovascular drugs	Adrenaline Noradrenaline Milrinone Atropine Glycopyrrolate Beta blockers Phenylephrine Magnesium Angiotensin 2 inhibitors Fibrinolytic drugs	Ephedrine	Vasopressin Metaraminol
Miscellaneous	Syntocin Carboprost Tranexamic acid Aprotinin		Dexamethasone Hydrocortisone Clopidogrel (has been used safely)

General anaesthesia

There are many agents available to allow a safe general anaesthetic in a patient with acute porphyria, but a safe technique must be accompanied by team awareness of the implications of the condition, appropriate preoperative preparation, and the availability of expert advice, ideally including a porphyria specialist. Depending on the patient and surgical complexities, the provision for critical care admission may be advised.

Classifying drugs as porphyria safe or unsafe is too simplistic; the duration of exposure and the absolute dose dictate whether an acute crisis is triggered and the severity of the crisis. Multiple confounding factors in the perioperative period mean that the trigger for a crisis may be unclear. Much work has been done to develop databases based on international experience. Table 4 gives a list of commonly used drugs and their safety profile.

Cardiopulmonary bypass has been carried out successfully in patients with porphyria, despite the physiological stress imposed by hypothermia, pump-induced haemolysis, blood loss, and exposure to numerous drugs, all of which could trigger development of a crisis.

Implications for pain management

Management of acute pain associated with neurovisceral crisis is one of the most important aspects of managing patients with porphyria. Patients having acute painful crises have high disease

activity and are therefore at risk of major deterioration if an unsafe analgesic is used. Based on collective clinical experience, the safety profile of different analgesics is well known, so even severe pain should be manageable with safe and effective agents. Table 4 details the safety profile of common analgesics. The safety of any agent should be confirmed using one of the drug databases listed in the Sources of further information section.

For severe pain associated with an acute crisis, i.v. morphine via a patient-controlled analgesia system (PCAS) provides rapid onset, titratable, effective, and safe analgesia. Meperidine can also be used safely; there is less experience using fentanyl PCAS, but it is reported as safe to use.[3] Offering regular prochlorperazine or ondansetron can help manage opioid-induced nausea.

Diclofenac should not be used as it is probably porphyrogenic.[10] Other simple analgesics, in accordance with the WHO analgesic ladder, are safe to use[9] and are helpful, in addition to morphine, during an acute crisis and to control pain between crises.

A small minority of patients will experience chronic neuropathic pain, associated with an ongoing level of disease activity. Gabapentin, pregabalin, and amitryptilline are safe drugs to treat neuropathic pain.[9]

Patients with undiagnosed porphyria may also present at chronic pain clinic for management of chronic abdominal, pelvic, or back pain. If these patients have any neurological, psychiatric, or other associated features listed in Table 3, a urine sample should be checked for PBG to exclude acute porphyria (see the previous section).

It is important to appreciate that abdominal pain in patients known to have porphyria may be due to additional pathologies, for example, appendicitis. A careful history, examination, and focused investigations should highlight these patients.

Summary

Although relatively uncommon, anaesthetists may be involved with the care of patients with porphyria during elective or emergency surgery, supportive treatment in critical care during an acute crisis or for pain management. The variable and non-specific symptoms and signs of the condition require clinicians to actively consider the diagnosis and to have a low threshold for checking urinary PBG levels.

Anaesthetists should be aware of the perioperative factors that may trigger or worsen an acute crisis, and in particular should know where to source up-to-date information on the safety of individual drugs. Management with i.v. haem arginate together with supportive measures can improve outcome.

Sources of further information

- www.cardiff-porphyria.org
- www.wmic.wales.nhs.uk/porphyria_info.php
- www.drugs-porphyria.org
- www.porphyria-europe.com
- www.porphyria.org.uk

Declaration of interest

None declared.

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Please see multiple choice questions 17–20.