Porphyria

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Introduction

The porphyrias are a group of inherited metabolic disorders caused by altered activities of enzymes within the heme biosynthetic pathway. Altered enzyme activity is mainly due to gene mutation or acquired inhibition of the enzyme. Porphyrias are rare and can be challenging to diagnose since symptoms are nonspecific. Furthermore, they present special anaesthetic challenges perioperatively, especially the gastrointestinal and neurological presentations of acute porphyric crisis. To meet these challenges, this review outlines porphyria pathophysiology, classifications, presentation, management, and the implications of these disorders to the anaesthetist.

Pathophysiology

The heme is metalloporphyrins made from a pyrrole ring and iron ion. It has multiple functions in the body: it is an oxygen and carbon dioxide transporter, it is part of the electron transport chain, and it is a cofactor of several enzymes. Normal heme biosynthesis is made in all tissues but predominantly occurs in the liver and bone marrow. The bone marrow accounts for approximately 80%, whereas the liver produces 20% of overall heme synthesis.[1]

The first step in heme synthesis is the rate-limiting step whereby succinyl-coenzyme A and glycine condense to form δ-aminolevulinic acid (ALA), catalysed by the ALA synthase (ALAS) enzyme found in the mitochondria (Figure 1). The ALAS requires pyridoxal-5'-phosphate (a derivative of vitamin B6) as a cofactor. It occurs in two isoforms that are coded by different genes (ALAS1 and ALAS2).[2] The gene for ALAS1 is found on Chromosome 3 and the enzyme is ubiquitous in all tissues. The ALAS2 is erythroid-specific and is produced by bone marrow erythroblasts. The gene for ALAS2 is located on Chromosome X and its mutations cause sex-linked sideroblastic anaemia or X-linked protoporphyria.

The ALAS is significantly lower than other enzymes in the pathway and varies in expression. Physiologically, heme has a negative feedback loop effect on ALAS activity, limiting the formation of porphyrinogens.[4] Subsequently, the suppression is defective on porphyrias, causing increased enzyme activity. An ALAS is implicated as a toxic molecule, especially to the neurons, and its
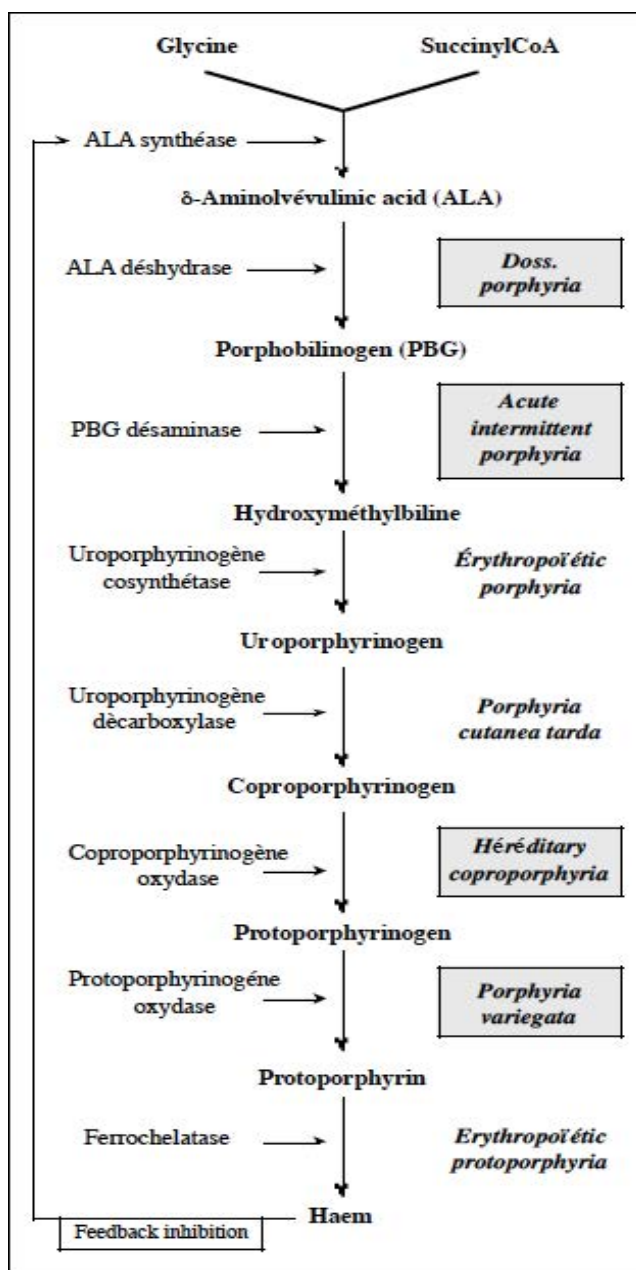

Figure 1: Heme biosynthetic pathway

accumulation is the proposed cause of symptoms in porphyria. The precise mechanism for neuropathy in porphyria is unknown and is a subject of debate. Two hypotheses have been proposed. The one mostly held states that ALA is neurotoxic and causes direct damage to autonomic ganglia, anterior horns of the spinal cord, and peripheral nerves. The second hypothesis suggests that a diminished intraneuronal heme level is responsible for neuropathy.

The first and last three enzymes are mitochondrial, while the other four are in the cytoplasm. All the genes that code these enzymes are in the cellular genome and inheritance of the porphyrias follows Mendelian genetic transmission rather than the mitochondrial.[3]

Therefore, the expressions of porphyria are due to increased ALAS activity, increased porphyrin (organic cyclical compounds found in heme) accumulation in the tissues, or decreased heme production.[5] The increased ALAS activity results in increased levels of heme precursors proximal to the site of the specific enzyme deficiency. These precursors are colourless porphyrinogens that can accumulate in the epidermal skin layers and cause cutaneous photosensitivity.[5]

Epidemiology

The prevalence of acute porphyrias in Europe is estimated to be 1–2 in 100 000, with acute intermittent porphyria (AIP) being the most common.[6] AIP is known as Swedish porphyria since the incidence is estimated to be 1 in 10 000 in Northern Sweden, while variegate porphyria (VP) is known as South African porphyria.[7] VP is common among the Afrikaner community and the prevalence is estimated at 1 in 250 to 1 in 500.[8] ALA dehydratase deficiency is very rare with less than 10 cases reported since 1979.[9] The actual incidence is challenging to assess as most patients remain asymptomatic. This is specifically the case with hereditary coproporphyria (HCP) where more than half the affected patients can be symptom-free.

Classification and presentation of porphyrias

Anaesthetists can be involved in the care of patients with porphyria during acute crisis, surgery, and pain management.[10]

The porphyrias may be classified according to three characteristics:

1. The site of abnormal porphyrin production (hepatic vs. erythropoietic) (Table I)
2. Acute or non-acute presentation
3. The pattern of enzyme deficiency in heme production

This classification reflects the pathophysiology and is useful for the anaesthetist since the acute forms of porphyrias may cause life-threatening reactions to drugs. The acute attacks are characterised by severe abdominal pain, autonomic instability, electrolyte disturbances, and neuropsychiatric manifestations. Neuromuscular weakness, quadriparesis, and respiratory failure is the most severe form of neuropathic dysfunction that can occur; however, seizures may also occur during the acute

Table I: Classification of porphyrias (Moore at el.[11])

Hepatic
1. *Hepatic acute porphyrias*
   a. Acute intermittent porphyria (AIP)
   b. Hereditary coproporphyria (HCP)
   c. Variegate porphyria (VP)
   d. ALA dehydrate deficiency porphyria
2. *Hepatic non-acute porphyria*
   a. Porphyria cutanea tarda (PCT)
      i. Familial
      ii. Acquired
   b. Hepatoerythropoietic porphyria (HEP)

Erythropoietic
1. *Erythropoietic porphyria*
   a. Uroporphyria
   b. Protoporphyria

attack. The abdominal pain is thought to be due to autonomic neuropathy since it is resolved with ganglionic block, though a block is rarely used as the treatment. Also, abdominal pain is severe with characteristic features of alternating areas of spastic and relaxed bowel and is associated with vomiting and diarrhoea. Clinically, the abdominal examination is mostly normal and disproportionate to the pain.

Dehydration and abnormalities of sodium, potassium, and magnesium can be severe and require adequate management during attacks. Lastly, cardiovascular instability such as tachycardia and hypertension occur particularly with AIP.

Diagnosis

The diagnosis requires a high index of suspicion because the patients are asymptomatic between attacks. A positive family history must raise suspicion and must be followed with laboratory investigation. The urinary and faecal assay of ALA, porphobilinogen (PBG), and porphyrins are used to make a diagnosis. During the latent phase the ALA, PBG, and porphyrins are normal in VP, while for AIP they are raised in both the latent and acute phases. The VP is mainly characterised by increased ALA, PBG, and porphyrins during the acute phase. Genetic testing is preferred in families with a positive family history of porphyria, and it is the most certain diagnostic procedure.[12]

Acute porphyric crisis

Acute attacks occur in only four types of porphyria: AIP, HCP, VP, and plumboporphyria (PLP).[13] Acute porphyrias have the potential to develop crisis, which can be generally triggered by fasting, dehydration, infection, drugs, and alcohol. Acute crises are more common in females than males and present during the third and fourth decades of life. The porphyria crisis can be challenging to identify since the signs and symptoms can be like other conditions such as endometriosis and pelvic inflammatory disease in females (Table II). Tachycardia is frequently a marker of disease state progression; as the heart rate increases the patient's condition generally deteriorates and the opposite is also true.

Table II: Symptoms and signs of acute crisis

Symptoms and signs	Clinical features
Gastrointestinal	Recurrent, severe, poorly localised abdominal pain. Associated with nausea and vomiting. Constipation and gastroparesis are secondary to autonomic dysfunction. Electrolyte disturbance, such as low sodium and magnesium.
Cardiovascular	Tachycardia, atrial fibrillation, hypertension, and postural hypotension.
Central nervous system	Weakness that is proximal more than distal and affects upper limbs more than lower limbs. May progress to respiratory paralysis and bulbar paresis. Seizures due to hyponatraemia. Pain in the back and thigh. Sensory neuropathy over the truck. Mental changes like confusion, mood changes, and psychosis.

The acute attack initiated by the drugs may occur during anaesthesia or perioperatively. Furthermore, drugs can trigger porphyria through four mechanisms:[14] induction of ALAS transcription, interfering with the negative feedback control of ALAS by heme, interfering directly with the heme synthetic pathway, and induction of cytochrome P450 causing high demand for heme. The identification of the drugs most likely to be a porphyric trigger can be difficult, hence the porphyria unit at the University of Cape Town, South Africa, maintains a database of drug safety. The centre can be contacted at www.porphyria.uct.ac.za. Internationally, multiple databases exist, such as the American Porphyria Foundation (www.porphyriafondation.org) and the European Porphyria Centre (www.drugs-pophyria.org).

Treatment

The management of porphyria consists of general, symptomatic/supportive, and targeted treatment. A general measure starts with the identification and elimination of the provoking drugs, hydration, and correction of the electrolytes, specifically hyponatraemia and hypomagnesaemia. The symptomatic treatment depends on the existing symptoms, which differ in each attack. Analgesia such as paracetamol and opioids are safe for pain relief.[15] Cardiovascular symptoms are successfully managed with beta blockers, such as propranolol. The use of diazepam for convulsions is contraindicated because it can induce a crisis. Convulsions are treated with clonazepam and magnesium sulfate, which may be less potent. Nausea responds well to prochlorperazine, ondansetron, and cyclizine; however, metoclopramide must be avoided. The 5% or 10% glucose solution is recommended since carbohydrates decrease ALAS activity.

The targeted treatment in the form of heme supplementation is indicated when there is neuropathy. The intravenous heme solutions are available in two forms, haematin and hemin (heme arginate), which are shown to cause fewer side effects.[16] It is given in a dose of 3 mg/kg, dissolved in 100 ml 0.9% sodium chloride, slowly for four days through a central line. Frequent heme infusions can cause chronic hepatic inflammation due to iron overload. Recently, the Food and Drug Administration (FDA) approved givosiran, a small interfering ribonucleic acid (siRNA) antagonist of ALAS, which is expected to prolong asymptomatic states and delay crises.[17]

Anaesthetic management

Anaesthetic management depends on the current condition of the patient; is the patient in remission or presenting with acute attacks? A patient in remission can safely undergo whichever type of anaesthesia (general and regional anaesthesia). During acute attacks, general anaesthesia is recommended over regional due to the risk of peripheral neuropathy.

In the preoperative period, attention must be focused on hydration, calorie intake, and the electrolyte status of the patient. The autonomic nervous system and cardiorespiratory function should be assessed. The anxiolytics such as midazolam and lorazepam are well tolerated.[8] Analgesia during acute porphyric crises can be achieved with morphine, fentanyl, sufentanil, and non-opioids like paracetamol, indomethacin, and aspirin are considered safe.

The induction and maintenance agent of choice in porphyria is propofol. Ketamine and etomidate show an impact on porphyria crisis onset in animal models; however, in clinical practice, they are considered safe in therapeutic doses.[18]

Volatile anaesthetics are used for the maintenance of general anaesthesia. Both sevoflurane and desflurane are safe even in prolonged administration. Halothane, nitrous oxide, and isoflurane have not caused adverse effects in porphyric patients; however, enflurane has shown porphyrinogen action and should be avoided.[19]

The muscle relaxants and reversals are well tolerated, and succinylcholine safety has been shown in both clinical practice and laboratory conditions.[20] Atracurium has been safely administered in a patient with AIP. The consensus is that muscle relaxants are safe for short-duration usage, but their safety for prolonged administration needs further analysis.

Conclusion

Porphyria has implications for the anaesthetist and anaesthetic drugs can trigger acute porphyric crises. They are challenging to diagnose, and a high index of suspicion needs to be maintained.

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