Twilight in the emergency department: Porphyria, mad kings, vampires and werewolves? A brief review

By Mark Mastin

Overview

The porphyrias are a group of disorders of the heme biosynthesis pathway (also known as the porphyrin pathway) that present with acute neurovisceral symptoms or skin lesions or both. Diagnosis is difficult and they are often missed or wrongly diagnosed (Thadani, Deacon, & Peters, 2000). Acute attacks may present with symptoms including severe abdominal pain (Anderson et al., 2005), hysteria (Millward, Kelly, King, & Peters, 2005), and motor neuropathies (weakness). As there is a very characteristic discrepancy between the serious complaints and the actual clinical findings, these patients can present a challenge to the emergency nurse (Liu et al., 2005; Tasnadi, Bor, Pusztai, & Szekely, 2003).

The name porphyria is derived from the Greek πορφύρα, *porphyra*, "purple pigment". The name is believed to have been a reference to the purple discolouration of feces and urine in patients during an attack (Lane, 2002).

Porphyrias are classified as acute (also known as hepatic) or chronic (also described as cutaneous or erythropoietic) (Forbes & Jackson, 1997).

Pathophysiology

Porphyrins is a group of organic compounds that occur in most living cells in both animals and plants. They are combined with metals such as magnesium in the plant kingdom to produce chlorophyll, and with iron in the animal kingdom to produce heme (Tobe, n.d.). Heme is critical for oxygen binding and transport for the cytochrome P-450 pathway, for activation and decomposition of hydrogen peroxide, for oxidation of tryptophan and prostaglandins, and for the production of cyclic guanine monophosphate (cGMP).

Heme is synthesized mostly in the bone marrow (85%) by erythroblasts and reticulocytes. Heme is also synthesized in the liver (15%) where it is primarily used for cytochromes and peroxisomes. Heme synthesis requires eight enzymes (Figure One). A deficiency or defect in any of the last seven enzymes of the heme biosynthetic pathway may result in its substrate, and any other heme precursors normally modified by that enzyme, accumulating in bone marrow, liver, skin, or other tissues producing toxicity.

Porphyrias can be inherited or (rarely) acquired (Champe & Harvey, 1994). With the exception of congenital erythropoietic

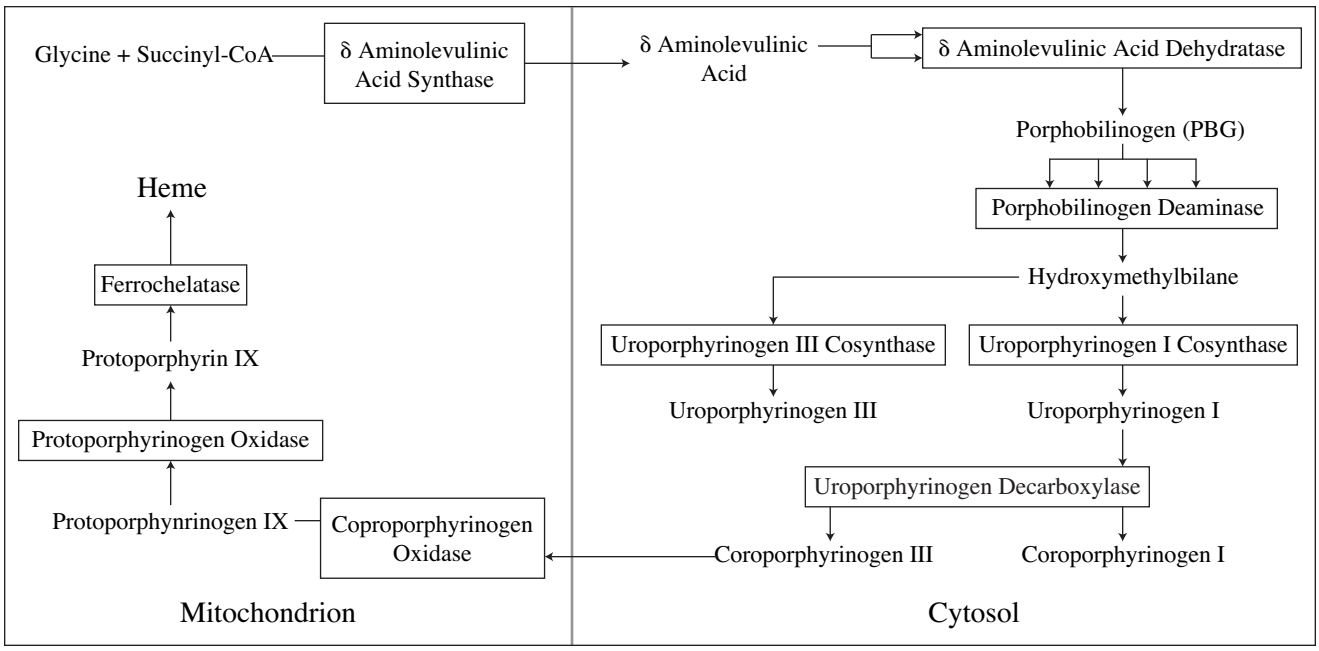

Figure One.

porphyria and aminolevulinate dehydratase deficiency porphyria, which are autosomal recessive, all other porphyrias are inherited as autosomal dominant disorders. The majority (an estimated 80% within families) of those who inherit an autosomal dominant porphyria remain asymptomatic; this is referred to as latent or presymptomatic porphyria. In acute intermittent porphyria, out of 100 patients with the genetic defect, perhaps 10 to 20 secrete excess porphyrin precursors and only one to two has symptoms (European Porphyria Initiative, 2003–2008).

The classic inducers of symptomatic porphyria are chemicals or situations that boost heme synthesis. This includes fasting, alcohol, endocrine factors, infection, smoking and many medications. Although very large lists of "safe" and "unsafe" drugs exist, many of these are based on anecdotes or laboratory evidence (Gorchein, 1997). In general, drugs that lead to increased activity of the hepatic P450 system, such as phenobarbital, sulfonamides, estrogens, and alcohol, are associated with porphyria. However, many attacks occur without any obvious provocation.

Prevalence

Acute porphyrias

The combined prevalence of the acute porphyrias is estimated at approximately five cases per 100,000 persons (Anderson, Sassa, Bishop, & Desnick, 2001) in the U.S. Prevalence of acute intermittent porphyria can be as high as 60 to 100 cases per 100,000 in northern Sweden (Bylesjo, Wikberg, & Andersson, 2009).

Cutaneous porphyrias

The United States has an estimated four cases per 100,000. Internationally, rates vary from 0.7 per 100,000 for hereditary coproporphyria in Israel to 34 per 100,000 in South Africans of Danish decent for variegate porphyria (Kirsch, Meissner, & Hift, 1998). Porphyria cutanea tarda is the most common porphyria—its prevalence is one in 25,000 in the U.K. (Elder, Smith, & Smyth, 1990).

Clinical manifestations

Clinical manifestations depend on the step in which the enzymatic defect occurs. If the enzymatic defects are in the initial steps of the metabolic cascade, early metabolic intermediates will accumulate, which are responsible for attacks of neurologic dysfunction. If the enzymatic defects are in the final steps, sunlight-induced cutaneous lesions (photosensitivity) due to porphyrin accumulation in the skin will develop (Canavese, Gabrielli, Guida, & Cappellini, 2002).

This photosensitivity is related to the fact that the protoporphyrin molecule has the ability to store radiant energy, usually ultraviolet light with a wavelength of about 400 nm. For the most part, this radiant energy is derived from exposure to bright sunlight. This energy build-up within the cells can damage the subcellular structures (Tobe, n.d.).

Acute porphyrias

The acute porphyrias are characterized by periodic acute attacks of neurovisceral symptoms and may stay occult for a long time. The three major disorders in this group are acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. Attacks are clinically indistinguishable in the three syndromes. The commonest is acute intermittent porphyria (Neuromuscular Disease Center, Washington University, n.d.).

Doss porphyria (aminolevulinate dehydratase deficiency porphyria), the fourth in this group, is extremely rare—a total of five cases reported in the literature by 2004 (Doss et al., 2004).

These porphyria syndromes are characterized by (Thadani et al., 2000):

- Psychiatric symptoms, such as hysteria, restlessness, psychosis (Ellencweig, Schoenfeld, & Zemishlany, 2006), insomnia or anxiety (Millward et al., 2005).
- Abdominal pain can resemble an acute abdomen and occurs in 95% of attacks (Kauppinen, 2005).
- Peripheral neuropathies, predominantly motor, can mimic Guillain-Barré syndrome. This may cause respiratory failure requiring mechanical ventilation.
- Coloured (dark or red) urine.
- Autonomic disturbance can cause nausea, vomiting (80%) and constipation.
- Central nervous system signs may consist of seizures (2.2% to 5.1%) (Bylesjo, Forsgren, Lithner, & Boman, 1996), mental status changes, cortical blindness, and coma.
- Sympathetic over-activity causes tachycardia (30% to 80%), arrhythmias, hypertension (50%) and postural hypotension.

Chronic porphyrias

The chronic or cutaneous porphyrias are dermatologic diseases that may or may not involve the liver and nervous system and do not present with acute attacks, as described for the acute porphyrias above. They may be chronic with only minimally bothersome intermittent problems that develop gradually over months and persist for years (Tobe, n.d.). These syndromes include congenital erythropoietic porphyria, erythropoietic porphyria, and porphyria cutanea tarda.

Patients may present with skin fragility, erosions, vesicles, bullae, and milia in sun-exposed areas of the skin. Sometimes, there is the presence of periorbital mottled hyperpigmentation and hypertrichosis, sclerodermoid changes, and ulceration.

Pseudoporphyria

Pseudoporphyria describes a bullous photosensitivity that clinically and histologically mimics porphyria cutanea tarda. However, no demonstrable porphyrin abnormalities are present. The commonest etiology is ingestion of various medications, such as Voriconazole (Tolland, McKeown, & Corbett, 2007), Nalidixic acid (Zelickson, 1964), and Furosemide (Burry & Lawrence, 1976). Ultraviolet A (UVA) exposure from sunbeds (Stenberg, 1990) and hemodialysis have also been implicated.

Treatment

- Oral and intravenous glucose suppresses the activity of aminolaevulinic acid synthase (the first enzyme in the heme pathway) and, therefore, reduces the overproduction of porphyrins and the precursors formed prior to the enzyme block (Li, 2005). At least 300g to 400g should be given in 24 hours. This may terminate mild attacks (Thadani et al., 2000).
- Meperidine or morphine parenterally to treat pain.
- Phenothiazines such as chlorpromazine can be used for nausea, vomiting, anxiety and restlessness.
- Propranolol or Nadolol, which can be safely used for beta blockade to treat tachycardia and/or hypertension.
- Magnesium (Sadeh, Blatt, Martonovits, Karni, & Goldhammer, 1991) and Gabapentin are used to treat seizures, as most classic antiseizure medicines can lead to acute porphyria attacks.
- Monitor for hyponatremia or hypomagnesemia and treat as needed.
- Institute cardiac monitoring, as arrhythmias are common.
- Hematin (Panhematin) is available in Canada through Special Access Canada for patients experiencing severe attacks, especially those with severe neurologic symptoms (Anderson & Collins, 2006). This provides negative feedback to the heme synthetic pathway and shuts down productions of porphyrins and porphyrin precursors.
- Avoidance of sunlight is the key in treating cutaneous porphyrias.
- Iron depletion can treat several of the cutaneous porphyries. Phlebotomy and apheresis can remove excessive iron in patients with porphyria cutanea tarda. Standard phlebotomy for adults consists of removal of 250 mL to 500 mL of blood once or twice per week (Poh-Fitzpatrick, Honig, Kim, & Sassa, 1992).

Historical and mythological aspects

Vampires and werewolves

Some vampire and werewolf legends have been thought to have arisen from porphyria, as there are certain similarities between the symptoms of the condition and folklore.

These theories have resulted in sometimes-acrimonious debate. Some claim that it sensationalizes the disease and stigmatizes the sufferers.

There have been associations drawn since the 15th century, but the first scientific paper was "On Porphyria and the Aetiology of Werewolves" (L. Illis), which was published in the Proceedings of the Royal Society of Medicine in January 1964. The 1973 book, "Vampires", by Nancy Garden presented arguments for a link between porphyria and the belief in vampires.

Biochemist David Dolphin's 1985 paper, "Porphyria, Vampires, and Werewolves: The Aetiology of European Metamorphosis Legends", published by the American Association for the Advancement of Science, received much media attention, popularizing the connection. Another important source for those interested in the subject is Norine Dresser's "American Vampires: Fans, Victims, Practitioners (1989)".

A cornerstone to the theory, the perceived harmful effect sunlight had on vampires, is, in fact, a recent addition to vampire lore. It originates from a 1922 German vampire film "Nosferatu, eine Symphonie des Grauens" (Nosferatu: A Symphony of Horror).

Mad kings

King George III of England had symptoms of abdominal pain, rashes, reddish urine, and psychotic episodes that are consistent with porphyria, although the account is disputed by many (Cooper & Powell, 2006).

The first suggestion that a physical illness was the cause of King George's mental derangements came in 1966, in a paper "The 'insanity' of King George III: A classic case of porphyria" (Macalpine & Hunter, 1966), with a second paper 1968, "Porphyria in the royal houses of Stuart, Hanover and Prussia" (Macalpine, Hunter, & Rimington, 1968). Many psychiatrists disagreed with the diagnosis, suggesting bipolar disorder as far more probable.

It has also been suggested that King Nebuchadnezzar of Babylon suffered from some form of porphyria (cf. Daniel 4) (Beveridge, 2003), as well as the proposal that Vincent van Gogh may have suffered from acute intermittent porphyria (Loftus & Arnold, 1991).

About the author

Mark Mastin moved to the Annapolis Valley from Calgary about a year ago. Mark is the assistant manager for emergency. He has spent the last 20 years working in large urban emergency departments—prior to that, he worked in various ICUs and a burn unit. He lives with his wife, four children, two dogs and a rabbit named "Calypso". He enjoys the peace and serenity of the emergency department.

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