Open Access Research Journal of
Life Sciences
Journals home page: https://oarjpublication/journals/oarjls/
ISSN: 2783-025X (Online)

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Porphyria: A metabolic disorder

Jennifer Ezinne Ugbala [1], Kingsley Uchechukwu Eke [2], Justice Obunda Nyeche [3], Mary Francisca Effiong [4], Chika Kalu Ndukwe [5], Oluwatosin Opeyemi Ogunwola [6], Chinwendu Vivian Achonwa [7], Chinenye Vivian Nwachukwu [8], Kosiso Johncross Omeje [8], Chukwu Chigozie David [9], Orume Maryam Sylvanus [10] and Ikenna Kingsley Uchendu [8,*]

[1] *Department of Medical Laboratory Science, Madonna University, Elele, Nigeria.*
[2] *Department of Medical Laboratory Science, Abia State University, Uturu. Nigeria.*
[3] *Department of Pharmacy, University of Port Harcourt, Nigeria.*
[4] *Department of the N.A Semashko public health and Healthcare, Erismann institute of public health, I.M Sechenov First Moscow State Medical university, Russia.*
[5] *Department of Medical Laboratory Science, Imo State University, Owerri, Imo State, Nigeria.*
[6] *Department of Medical Laboratory Science, Ladoke Akintola University of Technology, Ogbomoso, Oyo State Nigeria.*
[7] *Department of Medical Rehabilitation (Physiotherapy), Nnamdi Azikiwe University, Anambra State.*
[8] *Department of Medical Laboratory Science, University of Nigeria, Enugu Campus, Nigeria., Nigeria*
[9] *Department of Medical Laboratory Science, King David Federal school of medical sciences, Uburu Ebonyi State, Nigeria.*
[10] *Department of Geography, Nasarawa State University Keffi, Nasarawa State, Nigeria.*

Open Access Research Journal of Life Sciences, 2023, 05(02), 105–120

Publication history: Received on 29 April 2023; revised on 06 June 2023; accepted on 09 June 2023

Article DOI: https://doi.org/10.53022/oarjls.2023.5.2.0041

Abstract

Porphyrias are heterogenous group of metabolic disorders arising from defects in the heme biosynthetic pathway, each being characterized by a specific partial enzyme deficiency. Also, a flawed gene that control the action of enzyme in the heme synthesis creates a lack of heme and build up of porphyrin. Porphyria can be triggered by environmental factors such as; infections, cigarette smoking, antibiotics, etc. Porphyria can be classified into acute porphyria that causes neurological symptoms, and cutaneous porphyria that cause photosensitivity, affecting the skin. In cutaneous porphyria, the two distinct pattern of skin disease seen are the immediate photosensitivity and vesiculo-erosive skin disease. Symptoms include; abdominal pain, muscle weakness, hallucination, pain in the back or chest, burning pain on the skin, red or brown urine. Long term complication include paralysis, skin scarring, permanent hair loss, gall stones, breathing difficulties, dehydration. It can be diagnosed using blood, urine and stool samples, urine estimation of porphobilinogen is also done. Treatment of porphyria include; administration of heme arginate, regular blood removal, low doses of antimalarial drug, narrow band UVB therapy, avoidance of triggers. It can be prevented by avoiding factors that precipitate it such as; stress, fasting, infection, alcohol.

Keywords: Porphyrias; Metabolic disorder; Enzyme deficiency; Porphyrin; Porphobilinogen

1 Introduction

Porphyria refers to a group genetic disorder that affect the nervous system or the skin. Porphyria is a group of diseases in which substances called porphyrins build up, negatively affecting the skin or nervous system. It results from a build-up of natural chemicals that produce porphyrin in the body [1]. It is essential for the function of hemoglobin(a protein that links the porphyrin, binds iron and carries oxygen to the organs and tissues). High levels of porphyrin can cause significant problems. The types that affect the nervous system are also known as acute porphyria, as symptoms are rapid in onset and last a short time. Symptoms of an attack include abdominal pain, chest pain, vomiting, confusion, constipation, fever, high blood pressure, and high heart rate. The attacks usually last for days to weeks. Complications

* Corresponding author: Ikenna Kingsley Uchendu

may include paralysis, low blood sodium levels, and seizures. Attacks may be triggered by alcohol, smoking, hormonal changes, fasting, stress, or certain medications. If the skin is affected, blisters or itching may occur with sunlight exposure [2]. `

Porphyria can be categorized into acute, which mainly affects the nervous system and cutaneous, which mainly affects the skin. Its sign and symptoms vary depending on the type. Porphyria cannot be cured, but it can be managed by avoiding certain lifestyle that trigger symptoms. Treatment depends on the type of porphyria one has. The most common form is porphyria cutanea tarda (PCT) and is found in 1 in 10,000 people. Symptoms of the condition ranges from changes in skin pigmentation to hypertension [3].

Most types of porphyria are inherited from a person's parents and are due to a mutation in one of genes that make heme. They may be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner [4]. One type, porphyria cutanea tarda, may also be due to increased iron in the liver, hepatitis C, alcohol, or HIV/AIDS. The underlying mechanism results in a decrease in the amount of heme produced and a build-up of substances involved in making heme. Porphyrias may also be classified by whether the liver or the bone marrow is affected. Diagnosis is typically by blood, urine, and stool tests. Genetic testing may be done to determine the specific mutation [5].

Treatment depends on the type of porphyria and a person's symptoms. The treatment of porphyria of the skin generally involves the avoidance of sunlight. The treatment for acute porphyria may involve giving intravenous heme or a glucose solution [5]. Rarely a liver transplant may be carried out.

The frequency of porphyria is unclear. It is estimated that it affects 1 to 100 per 50,000 people. Rates vary around the world. Porphyria cutanea tarda is believed to be the most common type. The disease was described at least as early as 370 BC by Hippocrates. The underlying mechanism was first described by Felix Hoppe-Seyler in 1871. The name *porphyria* is from the Greek πορφύρα, *porphyra*, meaning "purple", a reference to the color of the urine that may occur during an attack.

2 Porphyria

The porphyrias are a heterogeneous group of metabolic disorders arising from defects in the heme biosynthetic pathway. Each porphyria is characterised by a specific partial enzyme deficiency . This leads to altered patterns of synthesis of porphyrins and their precursors, which accumulate and are linked to clinical manifestations[6]. Liu *et al.* reported that the majority of the body's heme is produced in erythroid cells and the liver. The rate of synthesis of the first intermediate in the pathway, 5aminolaevulinic acid (ALA), is important in controlling the formation of heme[7]. Ricci *et al.* reported that in the liver, the synthesis of ALA by ALA synthase is increased by increased demand for heme and, in turn, repressed by heme. Control of heme synthesis in the erythroid cells is more complex and ALA synthase is not repressed by heme [8]. Clinically porphyria can present with acute neurovisceral symptoms, skin lesions or both, depending on the specific enzyme deficiency [5].

2.1 Causes of porphyria

Each type of porphyria has the same root cause -- a problem in the production of heme. Heme is a component of hemoglobin. That's a protein in red blood cells that carries oxygen from the lungs to the rest of the body [9].

Heme is a red pigment composed of iron linked to a chemicals called protoporphyrin. Heme contains iron and gives blood its red color. The production of heme takes place in the liver and bone marrow and involves many different enzymes. A shortage of any of those enzymes can create an excess buildup of certain chemical compounds involved in producing heme. The specific type of porphyria is determined by which enzyme is lacking [5].

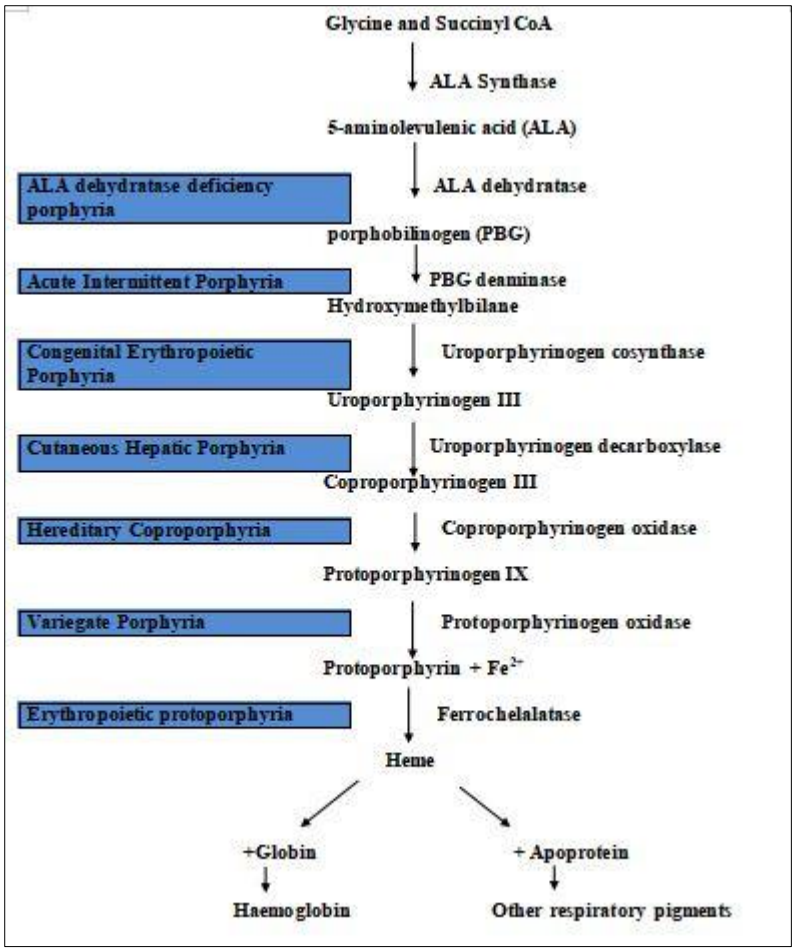

Figure 1 Heme biosynthesis and porphyria

Most types of porphyria are inherited. Most of those occur when one altered gene is passed from just one parent. The risk of developing a porphyria or passing it to your children depends on the specific type [4].

Porphyria cutanea tarda, on the other hand, is often an acquired disease [10]. Although the enzyme deficiency that causes PCT can be inherited, most people who inherit it never develop symptoms. Instead, the disease becomes active when the deficiency is triggered by certain conditions or lifestyle choices. These include:

- Drinking alcohol
- Estrogen use in females
- Hepatitis C
- HIV
- Smoking

Episodes of acute porphyria, which very rarely occur before puberty, can be triggered by some drugs [2]. These include:

- Barbiturates
- Sulfa antibiotics
- Birth control pills
- Seizure medicines

Other potential triggers include

- Fasting
- Smoking
- Drinking alcohol
- Infections

- Menstrual hormones
- Stress
- Sun exposure

Porphyria can be due to genetic factors or environmental factors.

2.1.1 Genetic cause of porphyria

The substance heme is used in various metabolic processes. The body makes heme from porphyrins which are metallic compounds found naturally in the tissue of animals. The conversion of porphyrins into heme requires the action of special proteins called enzyme. Genes control the action of enzymes. A flawed gene or genes stop the body from making one or more these enzyme. This creates a lack of heme and a buildup of porphyrin, which causes the signs and symptoms of porphyria [11].

Porphyria can be inherited in one of the following patterns:

- Autosomal dominant inheritance; where the faulty gene is inherited from one parent and it overrides the healthy gene inherited from the other parent.
- Autosomal recessive inheritance; where the faulty gene is inherited from the both parent.

2.1.2 Enviromental triggers of porphyria

There are some factors that triggers porphyria attack. These triggers vary from person to person. It may take time for an individual to discover their triggers for an attack. Each of these factors that triggers development of porphyria demands increased production of heme, which overwhelms the body's ability to deal with the increased level of porphyrin [12].

Common triggers include:

- Prescription of drugs such as barbiturates, sedatives, oral contraceptives and other type of antibiotics.
- Female sex hormone
- Excessive exposure to sunlight
- Heavy consumption of alcohol
- Cigarette smoking
- Infection
- Surgery
- Fasting
- Dieting
- Excess iron level

2.2 Pathogenesis

Heme synthesis—note that some reactions occur in the cytoplasm and some in the mitochondrion (yellow)

In humans, porphyrins are the main precursors of heme, an essential constituent of hemoglobin, myoglobin, catalase, peroxidase, and P450 liver cytochromes. The body requires porphyrins to produce heme, which is used to carry oxygen in the blood among other things, but in the porphyrias there is a deficiency (inherited or acquired) of the enzymes that transform the various porphyrins into others, leading to abnormally high levels of one or more of these substances. Porphyrias are classified in two ways, by symptoms and by pathophysiology [5].

Physiologically, porphyrias are classified as liver or erythropoietic based on the sites of accumulation of heme precursors, either in the liver or in the bone marrow and red blood cells [13].

Deficiency in the enzymes of the porphyrin pathway leads to insufficient production of heme. Heme function plays a central role in cellular metabolism. This is not the main problem in the porphyrias; most heme synthesis enzymes—even dysfunctional enzymes—have enough residual activity to assist in heme biosynthesis. The principal problem in these deficiencies is the accumulation of porphyrins, the heme precursors, which are toxic to tissue in high concentrations. The chemical properties of these intermediates determine the location of accumulation, whether they induce photosensitivity, and whether the intermediate is excreted (in the urine or feces) [14].

There are eight enzymes in the heme biosynthetic pathway, four of which—the first one and the last three—are in the mitochondria, while the other four are in the cytosol. Defects in any of these can lead to some form of porphyria[13].

The hepatic porphyrias are characterized by acute neurological attacks (seizures, psychosis, extreme back and abdominal pain, and an acute polyneuropathy), while the erythropoietic forms present with skin problems, usually a light-sensitive blistering rash and increased hair growth [13].

Variegate porphyria (also *porphyria variegata* or *mixed porphyria*), which results from a partial deficiency in PROTO oxidase, manifests itself with skin lesions similar to those of porphyria cutanea tarda combined with acute neurologic attacks. All other porphyrias are either skin- or nerve-predominant [15].

2.3 Classification/types of porphyria

Porphyria have different classification systems. The most accurate classification is by the specific enzyme deficiency.

Another classification is based on the primary origin of the excess precursors, it could be primarily in the liver as in hepatic porphyria, or primarily in the bone marrow as in erythropoietic porphyrias.

A third classification system distinguishes porphyria that cause neurological symptoms from those that cause photosensitivity. Based on this classification, porphyria is classified into two types thus;

- The Acute porphyrias
- The Non-Acute porphyrias

2.3.1 Acute porphyrias

This type primarily affects the nervous system. It causes damage to nerve cells due to the build up of raw chemicals that are typically used to make heme. It can also cause extreme discomfort. However, only 1 in 5 people who carry the gene for acute porphyria experience symtoms. Acute porphyria attacks are uncommon before puberty or after menopause and often difficult to diagnose [16].

Acute intermittent porphyria is the commonest type and has only acute attacks while the skin is not affected. In those who do not become ill, it appears that additional factors are required for an attack to occur, among these factors are a number of drugs and alcohol. However, acute attacks do occasionally occur in the absence of any identifiable factors [14].

Types of acute porphyria

- ALA dehydratase deficiency porphyria (ADP)
- Acute intermittent porphyria (AIP)
- Variegate porphyria (VP)
- Hereditary coproporphyria (HCP)

All the acute porphyrias, with the exception of ALA dehydratase deficiency porphyria (ADP) are inherited as an autosomal dominant trait. Yasuda *et al* [11] reported that ADP is inherited as an autosomal recessive condition.

In addition to the enzyme defect, clinical presentation of acute porphyria appears to require additional precipitating factors. These factors may affect the heme biosynthetic pathway by increasing the demand for heme, by causing further decreases in enzyme activity, or by a combination of these effects[14].

In very rare circumstances homozygous forms of each of the acute porphyrias have been described by Yasuda *et al* [11] and Wylie and Testai [14] as having simultaneous deficiency of two enzymes of the heme biosynthetic pathway, known as dual porphyrias.

- Acute intermittent porphyria

Zheng *et al*, [17] reported that this is the most common and severe of the acute porphyrias resulting from a deficiency of PBG deaminase, which acts as a second rate-limiting enzyme in the heme biosynthetic pathway. The activity of PBG deaminase is half normal, both in acute and latent cases [13].

As a result of the deficiency in PBG deaminase there may be excess formation and urinary excretion of the porphyrin precursors, ALA and PBG. Attacks are about five times more common in females than in male [5,17].

Clinical penetrance is low and patients may have no family history, the condition having remained latent or unidentified for several generations [5].

- Variegate porphyria

It results from a primary deficiency in the enzyme protoporphyrinogen oxidase, and a secondary deficiency in PBG deaminase [12]. Skin lesions, due to photosensitivity, have been reported to affect approximately 40% of gene carriers and are identical to those seen in porphyria cutanea tarda [18]. Lissing et al [19] reported that acute attacks tend to be less severe and less frequent than in AIP.

- Hereditary coproporphyria

Hereditary coproporphyria is the least common of the autosomal dominant acute porphyrias [20]. Phillips [13] reported that the primary enzyme deficiency is in coproporphyrinogen oxidase. As with variegate porphyria there is also a secondary deficiency in PBG deaminase as reported by Yasuda et al [11]. Clinical presentation is with acute attacks only (approximately 75%), or an acute attack accompanied by skin lesions (approximately 20%), [20].

2.3.2 Non-acute porphyrias or Cutaneous porphyria

This affects the skin and does not typically damage nerve cells. The build up of porphyrin in this type of porphyria causes oversensitivity to sunlight. It has less severe symptoms when compared to acute porphyria, but there are often occurrences of attack. Skin disease is encountered where excess porphyrins accumulate in the skin. Porphyrins are photoactive molecules, and exposure to light results in promotion of electrons to higher energy levels. When these return to the resting energy level or ground state, energy is released. This accounts for the property of fluorescence typical of the porphyrins. This causes local skin damage [2],

Examples of cutaneous porphyria are;

- Congenital erythropoietic porphyria(CEP)
- Porphyria cutaneous tarda(PCT)
- Erythropoietic protoporphyria(EPP)
- Hepatoerythropoietic porphyria

In all the cutaneous porphyrias, porphyrins (which are photosensitising) are deposited in the upper epidermal layer

Congenital erythropoietic porphyria

CEP, otherwise known as Gunther's disease is fortunately very rare. Both sexes are equally affected and patients present with severe photosensitivity, usually within the first few months of life according to Erwin *et al* [21] As a result of the photosensitivity they experience profound skin fragility which presents as blisters, erosions and scarring in sun-exposed areas as reported by Nahhas *et al*., [22]. These can progress to deformities and mutilations particularly on the face, hands and scalp, additionally they may develop secondary infections [21]. Haemolysis is common, leading to anaemia and secondary splenomegaly [22].

Porphyria cutanea tarda or cutaneous hepatic porphyria

PCT is the most common cutaneous porphyria. Erwin and Balwani [15] reported that in PCT a deficiency in hepatic uroporphyrinogen decarboxylase results in the accumulation of large amounts of photoactive porphyrins which are released into the circulation. It can be an inherited or more commonly an acquired disease and is manifested as skin fragility and blisters in light-exposed areas [21], erosions, scarring alopecia, pigmentary changes and hypertrichosis [21].. Liver disease including hepatocellular carcinoma is common according to Ramai *et al*., [23] (2022).

Erythropoietic protoporphyria

EPP is the second most common type of porphyria and usually presents in early childhood with painful photosensitivity. Phillips [13] reported that the disease manifests itself with urticarial lesions, oedema and sometimes painful petechiae. Nahhas *et al*., [22] also stated that chronic changes include linear scarring and waxy thickening of the skin. Systemic

complications maybe present such as anaemia, cholelithiasis, and liver dysfunction, which may rarely result in hepatic failure.

2.4 Two distinct patterns of skin disease are seen in porphyria:

- Immediate photosensitivity. This is typical of XLDPP and EPP. Following a variable period of sun exposure—typically about 30 minutes—patients complain of severe pain, burning, and discomfort in exposed areas. Occasionally there may be some redness and swelling of the skin [22].
- Vesiculo-erosive skin disease. This—a reference to the characteristic blistering (vesicles) and open sores (erosions) noted in patients—is the pattern seen in CEP, PCT, VP, and HCP. The changes are noted only in sun-exposed areas such as the face and back of the hands. Milder skin disease, such as that seen in VP and HCP, consists of increased skin fragility in exposed areas with a tendency to form blisters and erosions, particularly after minor knocks or scrapes. These heal slowly, often leaving small scars that may be lighter or darker than normal skin. More severe skin disease is sometimes seen in PCT, with prominent lesions, darkening of exposed skin such as the face, and hypertrichosis: abnormal hair growth on the face, particularly the cheeks [15].

Table 1 Subtypes of porphyrias depend on which enzyme is deficient

Porphyria type	Deficient enzyme	Type of porphyria	Inheritance	Symptoms	Prevalence
X-linked dominant protoporphyria (XLDPP)	5-aminolevulinate (ALA) synthase (ALAS)	Erythropoietic	X-linked dominant	Photosensitivity, cirrhosis	Rare; about 50 cases reported
Aminolevulinate dehydratase deficiency porphyria (ALADP)	5-aminolevulinate dehydratase (ALAD)	Hepatic	Autosomal recessive	Abdominal pain, neuropathy	Extremely rare; fewer than 10 cases ever reported
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase (HMBS), formerly porphobilinogen deaminase (PBGD)	Hepatic	Autosomal dominant	Periodic abdominal pain, peripheral neuropathy, psychiatric disorders, tarchycardial	1 in 10,000-20,000
Congenital erythropoietic porphyria (PCT)	Uroporphyrinogen synthase (UROD)	Erythropoietic	Autosomal recessive	Severe photosensitivity with erythma,swelling and blistering, hemolytic anaemia, splenomegaly	1 in 1,000,000 or less
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase (UROD)	Hepatic	Approximately 80% sporadic, 20% autosomal dominant	Photosensitivity with vesicles and bullae	1 in 10,000
Hereditary coproporphyria	Coproporphyrinogen oxidase (CPOX)	Hepatic	Autosomal dominant	Photosensitivity, neurologic symptoms, colic	1 in 500,000
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)	Hepatic	Autosomal dominant	Photosensitivity, neurologic symptom, developmental delay	1 in 300 in South Africa, 1 in 75,000 in Finland

Erythropoietic protoporphyria (EPP)	Ferrochelatase (FECH)	Erythropoietic	Autosomal dominant	Photosensitivity with skin lesions. Gall stones, mild liver dysfunction	1 in 75,000-200,000
Harderoporphyria	Coproporphyrinogen oxidase (CPOX)	Erythropoietic	Autosomal dominant	Jaundice, anaemia, enlarged liver and spleen, often neonatal, photosensitivity later	Extremely rare; fewer than 10 cases ever reported

2.5 Symptoms of porphyria

Symptoms of porphyria depends the type of porphyria

2.5.1 Acute porphyria symptoms

The condition mostly affects the nervous system. The skin occasionally is affected. The symptoms of acute porphyria can develop quickly and last for days or weeks. A salt imbalance sometimes accompanies an episode of this type of porphyria. The imbalance can contribute to some of these symptoms:

- Abdominal pain: this is often severe. It commonly mimics abdominal crisis [14]. It is often associated with constipation, nausea and vomiting[12]
- Cardiovascular features: hypertension and tachycardia are common, occurring in around two thirds of patients[24], hypertension may become chronic [25] and require treatment.
- Arrhythmias, a sign of progressive autonomic neuropathy, may result in sudden death as reported by Ma *et al*., [25].
- Muscle weakness and associated loss of sensation over the trunk and thigh may occur as a result of motor neuropathy, this can progress to respiratory failure [26].
- Wylie and Testai [14] reported that convulsions may occur and may be associated with hyponatraemia, which can occur in up to 40% of acute attacks.
- Psychiatric changes that may be present during acute attacks include;
  - Confusion
  - Disorientation
  - Hallucinations
  - Paranoia
- In an acute attack, passed urine may become dark on standing, due to the conversion of PBG to a brownish-red pigment porphobilin as reported by Wang et al., [27]. Non-enzymatic formation of these coloured compounds is promoted by exposure to light, heat and an acid pH.1
- Pain in the back, abdomen, chest or limb
- Increased heart rate and blood pressure
- Impaired movement of the limb
- Electrolyte attack
- Muscle pain or paralysis

Long term complication in patients may include;

- Chronic pain
- Depression
- Kidney damage
- Liver cancer

2.5.2 Cutaneous/chronic porphyria symptoms

Here, the skin is affected and not the nervous system. Symptoms of cutaneous porphyria occur when the skin is exposed to sunlight. The most commonly affected areas include the back of the:

- Hands
- Forearms

- Face
- Ears
- Neck

Cutaneous porphyria attacks occur as a result of exposure to sunlight and can last several days. Symptoms may include;

- Itching
- Red or brown urine
- Lasting blisters
- Burning pain on the skin
- Redness or swelling on the skin
- Increased hair growth
- Darkening and thickening of the skin

Generally, the possible symptoms of porphyria both for acute and cutaneous is the unusual colour of urine. Both forms can cause long-term complications among which are:

- Liver or kidney failure
- High blood pressure
- Breathing difficulties
- Gallstones
- Permanent skin damage
- Muscle weakness
- Paralysis
- Permanent hair loss
- Skin scarring
- Dehydration
- Low salt level in the blood(hyponatraemia)

Figure 2 Scarring of the mouth and tongue

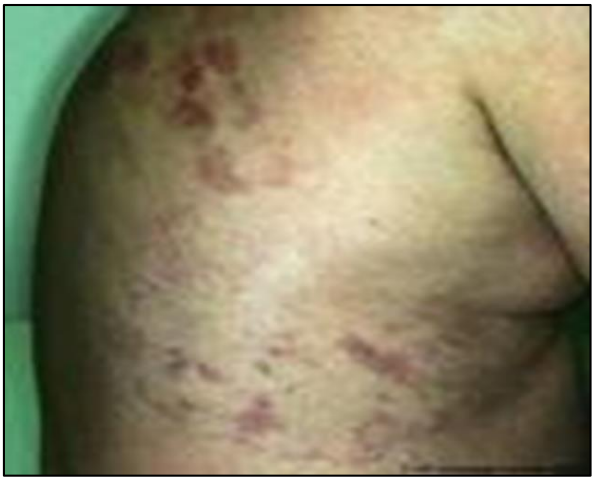

Figure 3 Redness of the skin

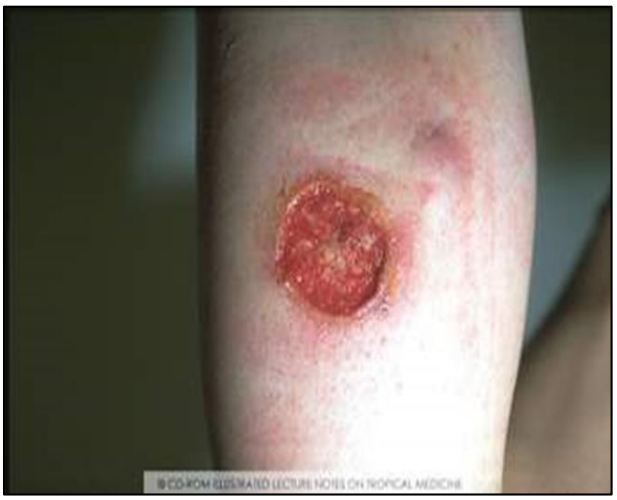

Figure 4 Burning pain on the skin

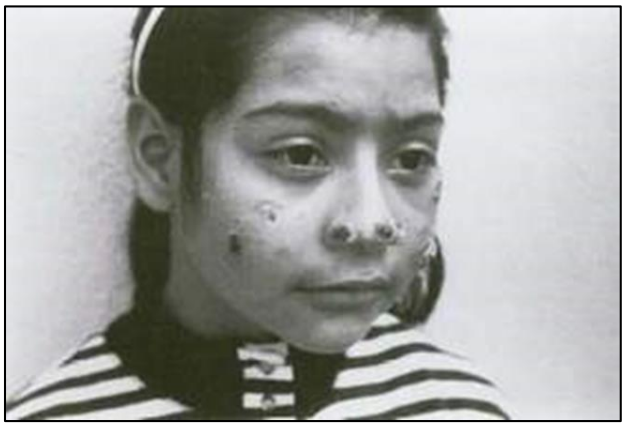

Figure 5 Lasting blisters

2.6 Diagnosis

Blood, urine, and stool tests are performed to diagnose porphyria. The best time to be tested is during an outbreak of symptoms or around the time of them.

Sometimes multiple tests will be required before the diagnosis of a particular type of porphyria is possible. Because porphyria often runs in families, other family members can be tested and counseled after a positive diagnosis [4].

Porphyria is diagnosed through biochemical analysis of blood, urine, and stool. In general, urine estimation of porphobilinogen (PBG) is the first step if acute porphyria is suspected. As a result of feedback, the decreased production of heme leads to increased production of precursors, PBG being one of the first substances in the porphyrin synthesis pathway. In nearly all cases of acute porphyria syndromes, urinary PBG is markedly elevated except for the very rare ALA dehydratase deficiency or in patients with symptoms due to hereditary tyrosinemia type I. In cases of mercury- or arsenic poisoning-induced porphyria, other changes in porphyrin profiles appear, most notably elevations of uroporphyrins I & III, coproporphyrins I & III, and pre-coproporphyrin [5].

Repeat testing during an attack and subsequent attacks may be necessary in order to detect a porphyria, as levels may be normal or near-normal between attacks. The urine screening test has been known to fail in the initial stages of a severe, life-threatening attack of acute intermittent porphyria [28].

If all the porphyrin studies are negative, one must consider pseudoporphyria. A careful medication review often will find the cause of pseudoporphyria.

2.6.1 Additional tests

Further diagnostic tests of affected organs may be required, such as nerve conduction studies for neuropathy or an ultrasound of the liver. Basic biochemical tests may assist in identifying liver disease, hepatocellular carcinoma, and other organ problems [29]..

2.7 Management/treatment

2.7.1 Management of acute attacks

Patients in acute attacks should have regular monitoring of pulse, blood pressure and respiratory rate. Any drugs used during an acute attack should be safe to use in acute porphyrias.

Specific treatment

Heme arginate should be administered by intravenous infusion over at least 30 minutes in 100ml of sodium chloride0 0.9%. Its dose is 3mg/kg(to a maximum of 200mg) one day for four consecutive days. Heme arginate replenishes the body's own heme stores. Through negative feedback, it inhibits ALA synthase, thus reducing the production of poyphyrins and other precursors, ALA and PBD. Because heme arginate is a dark solution, making it difficult to check for absence of particle, it is adviced to administer using a 15-20 micron in-line filter [30]. (Fernandez et al., 2020)

Supportive treatment

- Removal of precipitating factors: any drug known to be unsafe in the acute porphyria should be discontinued. Other potential risk factors such as infection should be treated.
- Nutrition: adequate calories should be given.
- Hypertension can be controlled with beta-blockers such as propranolol, labetalol
- Neurosis and psychosis require sedatives or tranquiliser example, lorazepam, and/or chlorpromazine [31] (Prescilla, 2021)
- Seizure should be treated intravenously with lorazepan, clonazepam [32].
- In constipation, Laxatives such as bulk-forming Lactulose Senna should be given.
- Vomiting should be treated with promazine,
- Abdominal Pain, Analgesics such as aspirin, diamorphine, dihydrocodeine ,ibuprofen, morphine, paracetamol ,pethidine should be given.
- In case of skin photosentivity, sunlight should be avoided [12].

Management of symptoms should be individualised to meet the needs of the patient.

General anaesthesia in patients with acute porphyria

General anaesthesia poses the greatest risk to patients whose porphyria is or has been recently active. However, general anaesthesia may be undertaken safely providing appropriate safe drug choices are made for the procedure. Also any resulting infection(s) should be treated aggressively to avoid post-operative porphyria complications. Patients should avoid a pre and post-operative starvation [26].

2.7.2 Management of cutaneous porphyria

Treatment of cutaneous porphyria can include:

- Regular blood removal (phlebotomies) to reduce the amount of iron in the liver.
- Low doses of the antimalarial drug such as chloroquine or hydroxychloroquine.
- Avoidance of triggers.
- Treatment of any underlying condition such as HIV or hepatitis C.
- Avoidance of sun [12].
- Narrow band UVB therapy.[12].
- Sunblocks containing zinc oxide and/or titanium dioxide (e.g. Dundee Sun Screen,).
- Oral beta carotene is advocated to increase sunlight tolerance,16 in doses of 120-300mg per day in divided doses. Monitoring is recommended to ensure adequate plasma levels are reached (11-15 micromoles/L).
- When liver dysfunction is present, measures taken to reduce plasma protoporphyrin levels include colestyramine [33], and chenodeoxycholic acid, [34] activated charcoal [33] and hyper-transfusion. Ultimately liver transplantation may be required in some cases [27].

Prescribing in non-acute porphyrias

Porphyria cutanea tarda, erythropoietic protoporphyria and congenital erythropoietic porphyria are non-acute porphyrias.

- If patients have unequivocally been diagnosed as having erythropoietic protoporphyria or congenital erythropoietic porphyria there are thought to be NO UNSAFE DRUGS since acute attacks are not encountered.
- For patients diagnosed with porphyria cutanea tarda, all drugs are SAFE except:
- Chloroquine and related drugs in antimalarial doses for both treatment and prophylaxis [12].
- Oestrogens (natural and synthetic) may provoke symptoms (skin lesions) and should not be prescribed until the disease has been brought into remission.

Non-acute porphyrias and antimalarials

Chloroquine is the only antimalarial to be avoided in porphyria cutanea tarda.

Female patients with acute porphyria: additional considerations. According to Pischik et al. [35], (2019), women are five times more likely than men to experience an acute porphyria attack. Endogenous hormones, particularly progesterone are important precipitants of acute attacks, which may partially explain this increased incidence and why attacks are more common during the luteal phase of the menstrual cycle [36].

2.8 Prevention of acute attacks (including advice to patients)

- Acute attacks are commonly precipitated by factors which increase demand for heme in the liver Wang [37] reported that events which may precipitate this do so by increasing the activity of ALA synthetase and stimulating the production of heme precursors (PBG and ALA).
- A number of factors can cause acute exacerbations and patients should be counselled about them, including:-
  - Physiological hormone fluctuations e.g. menstrual cycle
  - Fasting/dieting (if weight loss is required the advice of a dietician should be sought)
  - Stress
  - Infection
  - Alcohol should be restricted and smoking discouraged.
- Screening of families: Relatives of affected patients should be offered screening for acute porphyrias. This can be undertaken at any age. Children should be tested before puberty and testing with parental consent is therefore considered ethical.

2.9 Epidemiology

Rates of all types of porphyria taken together have been estimated to be approximately one in 25,000 in the United States. The worldwide prevalence has been estimated to be between one in 500 and one in 50,000 people.

The exact prevalence of acute porphyrias is difficult to determine. Clinically overt cases are rare. However, it is well known that the clinical penetrance of the disease is low, with 80 to 90% of carriers of the relevant gene defects remaining asymptomatic [38]. A study in healthy French blood donors assessed the prevalence of the gene mutation for AIP to be 1:1675 [39]. In most European countries it is estimated that 1-2 per 100,000 of the general population experience an acute porphyria attack [40]. The prevalence of the type of acute porphyria also varies in certain populations. Variegate porphyria is about a third less common [12], except among the Afrikaner population in South Africa, where the estimated prevalence is between 1 per 250 and 1 per 500 population [41]. Hereditary coproporphyria is the least common of the autosomal dominate acute porphyrias.[42].

2.10 General advice

In acute porphyria, where possible, SAFE drugs should be selected. However, if an unsafe drug needs to be used, for example, where no alternative exists or in a life threatening illness, the drugs may be administered with caution.

Unsafe drugs should be administered under close supervision with measurements of urinary porphobilinogen (PBG) before and every 2-3 days after giving the drug. If PBG excretion increases, the drug should be stopped.

2.10.1 Selecting a drug

- Always select the safest alternative, for example, there is little justification for prescribing erythromycin or a tetracycline if a penicillin would work just as well.
- Where there is no alternative, firstly, it is worth confirming that the diagnosis of acute porphyria is robust. Some patients may have been informed that they have porphyria based on equivocal investigations performed many years ago or due to misinterpretation of porphyrin measurements. If there is any doubt, it may be possible to arrange retesting. Should they not have acute porphyria, prescribing becomes easier.
  Where porphyria is confirmed, or it is not possible to exclude the diagnosis, one must make a risk-benefit decision. Is the expected result from the drug therapy sufficiently important to the patient's health to risk an acute attack? If not, refrain from prescribing. If so, the following is recommended:-
- Select the safest drug.
- Warn the patient that the drug you are prescribing cannot be guaranteed safe and obtain their consent to use it.
- Advise patient to stop the drug immediately and seek medical advice should they develop severe abdominal pain or darkening of the urine.
- Consider measuring urinary PBG levels before and during treatment, if they rise significantly the drug should be stopped.

2.10.2 Travelling with porphyria

In general, travel vaccines are considered safe in the acute porphyrias. However, there has been an unpublished report of an acute porphyria attack following yellow fever vaccination and therefore, caution may be warranted when administering live vaccines. According to Le *et al*. [43], the following antimalarials are suitable for use:

- Chloroquine
- Malarone® (atovaquone and proguanil)
- Mefloquine
- Proguanil

To minimise the risks of experiencing an acute attack, porphyria sufferers should be adviced to maintain adequate hydration by drinking plenty of non-alcoholic fluids. They should be advised not to miss meals and to consume meals with high carbohydrate content.

2.10.3 Gonadotropin-releasing hormone analogues

Therapy should be started within the ten days after the start of a menstrual period to minimise the associated hormone surge which can cause an acute attack. It is recommended that gynaecological examinations and bone density

determinations should be carried out every six months during treatment [44]. Treatment with a gonadotropin-releasing hormone analogue should be continued for at least 18 months.

2.10.4 Pregnancy and porphyria

Although pregnancy results in an increased level of progesterone it is well tolerated in most women according to Wang *et al.* [38], and does not appear to be a major risk to the patient with porphyria [16]. However patients with recurrent acute attacks are usually advised to avoid pregnancy until their disease enters a latent phase.

3 Conclusion

Porphyrias are heterogenous group of metabolic disorders arising from defects in the heme biosynthetic pathway, each being characterized by a specific partial enzyme deficiency. Porphyria can be classified into acute porphyria that causes neurological symptoms, and cutaneous porphyria that affects the skin. In cutaneous porphyria, the two distinct pattern of skin disease seen are the immediate photosensitivity and vesiculo-erosive skin disease. Symptoms include; abdominal pain, muscle weakness, hallucination, pain in the back or chest, burning pain on the skin, red or brown urine. Long term complication include paralysis, skin scarring, permanent hair loss, gall stones, breathing difficulties, dehydration. It can be diagnosed through urine estimation of porphobilinogen. It can be treated by administration of heme arginate, regular blood removal, narrow band UVB therapy and can be prevented by avoiding precipitating factors such as; stress, infection and alcohol.

Compliance with ethical standards

Acknowledgments

The authors acknowledge the authors whose works were cited in this narrative review.

Disclosure of conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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