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# PORPHYRIAS: TYPES AND TREATMENT

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## ABSTRACT
Porphyrins are metabolic disorders of the heme biosynthesis. Porphyrins are essential for the function of hemoglobin, a protein present in the red blood cells that is linked to porphyrin, and binds with iron thus carrying oxygen to the organs and tissues. Clinically they can be differentiated into acute and non-acute porphyrias. But the lack of awareness and adequate knowledge about the clinical features of porphyria results in delayed diagnostic and therapeutic outcomes in the patient. Porphyrias still remain undiagnosed, although the examinations of plasma and urine are the first line tests for the detection of excess amounts of porphyrin in the body. This review discusses about the porphyria and its metabolism, different types of porphyria with its clinical manifestations and therapeutic management of porphyria.

**KEYWORDS:** Porphyria, Porphyrin, Hepatic porphyria, Erythropoietic porphyria, Aminolaevulinic acid (ALA), Porphobilinogen, Photosensitivity, Phlebotomy.

## INTRODUCTION
The porphyrias are the heterogenous groups of rare, mostly inherited metabolic disorders which are caused due to the deficiency of specific enzymes in the heme biosynthetic pathway. Each porphyria is characterised by the deficiency in specific partial enzyme. This substantially leads to alteration in the synthesis of porphyrins and their precursors, which accumulate and are linked to clinical manifestations.[1] These disorders are generally classified as either hepatic or erythropoietic based on the primary site of overproduction and the accumulation of the porphyrin precursor or porphyrin. The major manifestations for the hepatic porphyrias are neurologic including neuropathic abdominal pain, neuropathy and abdominal disturbances, whereas the erythropoietic porphyrias causes cutaneous photosensitivity. Physicians must be aware of porphyrias, which could be responsible for the unidentified and unexplained gastrointestinal, neurologic, or skin disorders. Despite their complexity, they could be easily defined and diagnosed.[2]

### Porphyrin metabolism
The porphyrin- heme pathway is ubiquitous in the biological system. Its activity is regulated in such a way that large amounts of the end product heme are formed daily but the intermediates of the pathway accumulate and are eliminated only in trace amounts. It is thought that the bone marrow and liver are the body compartments in which this heme synthesis occurs.[3] Bone marrow requires heme for daily erythrocyte haemoglobin production and the hepatic heme for haemoproteins with relatively rapid turnover. Since heme cannot be reutilized and it is then broken down into linear tetrapyrroles that eventuate in bilirubin production. Thus, the body is continuously synthesizing heme.[4]

In human physiology, heme is very essential in the production of porphyrins. While considering its biologically active form, heme bounds tovarious proteins to form hemoproteins, which include hemoglobin, myoglobin and all of the cytochromes (including the $P_{450}$ series) together with various other compounds that are involved in the oxidation and hydroxylation reactions. The biosynthesis of heme begins with the formation of aminolaevulinic acid (ALA) by the condensation and subsequent decarboxylation of two freely available molecules (succinyl co-enzyme A (succinyl CoA) and the amino acid glycine). This step is catalyzed by the enzyme ALA synthetase. This step takes place in the mitochondria. The most important rate-limiting enzyme in porphyrin biosynthesis is ALA synthetase.[5] The next step in porphyrin synthesis takes place outside the mitochondria where two molecules of ALA condense under the presence of the enzyme ALA dehydratase to

form the monopyrrole subunit of the porphyrin ring, i.e., porphobilinogen (PBG). Then the enzyme PBG deaminase catalyses the condensation of four molecules of PBG to form hydroxymethylbilane. It is then converted into porphyrinogens, uroporphyrinogen, under the presence of uroporphyrinogen cosynthetase. The stepwise decarboxylation and conversion of uroporphyrinogen acetate groups to methyl substituents results in the production of coproporphyrinogen. Coproporphyrinogen re-enters the mitochondria undergoing oxidation and chelation with ferrous iron resulting in the production of heme.[6] The porphyrin biosynthetic pathway operates very efficiently. Only less than 2% of the porphyrin precursors are produced in excess amount than the required heme synthesis. But if there is an increased concentration of porphyrin intermediates present in urine or stool it indicates an abnormality of production, with a partial block somewhere in the enzymatic chain.[7]

**Control of heme biosynthesis**

The production of heme is primarily affected through ALA synthetase. This enzyme has low endogenous activity and has very short half-life. It is readily inducible and responds spontaneously to increased heme requirements such as those occurring due to administration of drugs that require cytochrome P450 for their active metabolism. Thus, the activity and availability of the enzyme depends on the intracellular level of the haem. This fact is of great importance in the development of the different types of porphyria. The defects in enzymes of the haem biosynthesis pathway are the underlying reason for the abnormalities that occur in the porphyria. The accumulation of porphyrin and porphyrin precursor and its excretion in excessive amounts are due to these enzyme defects. This can be illustrated through various studies such as in case of the protoporphyria and variegate porphyria.[8]

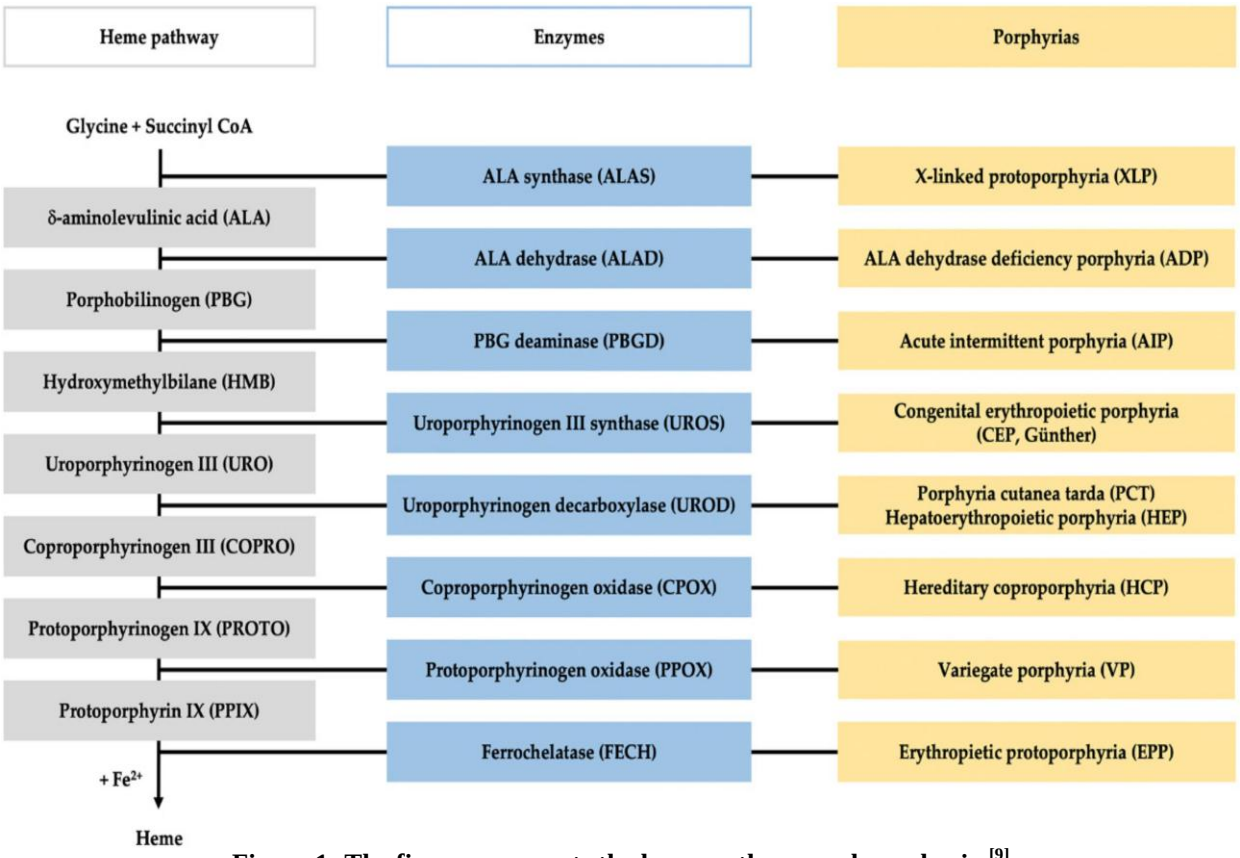


**Figure 1: The figure represents the heme pathway and porphyria.[9]**

**Classification of porphyria**

The porphyrias are generally classified into two groups depending upon the main organ where the abnormal porphyrin synthesis occurs (hepatic or erythropoietic porphyrias). The major clinical manifestations for the hepatic porphyrias are neurologic including neuropathic abdominal pain, neuropathy and abdominal disturbances, whereas the erythropoietic porphyrias causes cutaneous photosensitivity. Other classification is based on the genetics of these defects such as recessive, dominant or non-hereditary porphyria. But however, based on their clinical expressions, the porphyria could be divided into three groups:

A. Acute porphyrias
1. Acute intermittent porphyria (AIP)
2. Porphyria due to porphobilinogen -synthase deficiency (PBG-S)

B. Cutaneous porphyrias
1. Porphyria cutanea tarda (PCT)
2. Erythropoietic protoporphyria (EPP)

3. Congenital erythropoietic porphyria (CEP)
4. Hepatoerythropoietic porphyria (HEP)

C. Mixed porphyrias

1. Porphyria variegate (PV)
2. Hereditary coproporphyria (HCP)[10]

**A. Acute porphyrias**

Acute porphyrias include the forms of disease that typically affects the nervous system which appear quickly and can be severe. Symptoms may last from days to weeks. It usually improves slowly after the attack. Acute intermittent porphyria is the common form of acute porphyria. Acute porphyrias result from the deficiency of certain enzymes in the heme biosynthetic pathway. Patients are presented with acute debilitating, life-threatening attacks that may be precipitated by medications, hormonal changes, starvation and other factors.

**Acute intermittent porphyria (AIP)**

The defective enzyme in this condition is porphobilinogen deaminase and the gene coding for this enzyme is present on chromosome 11. It is a rare metabolic disorder and this deficiency result in the accumulation of porphyrin precursors in the body. Acute intermittent porphyria causes abdominal pain and neurologic symptoms. Many people never experience symptoms. This defect can occur in people of all ethnic groups. In most countries, it is the most common form of the acute porphyrias.

**Porphyria due to porphobilinogen -synthase deficiency (PBG-S)**

Delta-aminolaevulinic acid dehydratase (ALAD) which is also known as porphobilinogen synthase, catalyses the second step of the heme synthesis. Deficiency of this enzyme produces porphyria. It is characterized by autosomal recessive inheritance and produce only neurovisceral manifestations. In this defect, the enzyme activity is less than 3% when compared with the normal enzyme activity.[11]

**B. Cutaneous porphyrias**

Cutaneous porphyria includes forms that cause skin symptoms as a result of sensitivity to sunlight, but these forms don't usually affect the nervous system. As a result of sun exposure, the patient may experience sensitivity to the light, sudden painful skin redness, blisters on exposed skin, itching and excessive hair growth in the affected areas. The treatment can help, but cannot cure this condition completely. The emergency care is needed in severe cases.

**Porphyria cutanea tarda (PCT)**

PCT is a rare disorder characterized by painful, blistering skin lesions that develop on sun exposed skin. It arises as a result of abnormal enzyme present during the biosynthesis of heme. It is caused due to the deficiency of the uroporphyrinogen III decarboxylase (UROD) enzyme. It is known by other names like symptomatic porphyria, idiosyncratic porphyria, chemical porphyria or acquired hepatic porphyria. Approximately 80% of PCT are acquired, less than 20% are familial.

**Erythropoietic protoporphyria (EPP)**

It is an inherited porphyria resulting due to the accumulation of protoporphyrins or in red blood cells that causes acute, painful photosensitivity and potential liver disease. The most common manifestation is hypersensitivity of the skin to sunlight with pain, itching or burning of the skin after sun exposure and occasionally to fluorescent light. It is a rare inherited metabolic disorder caused by the deficiency of the enzyme ferrochelatase (FECH) which causes mutations in the FECH gene.

**Congenital erythropoietic porphyria (CEP)**

It is a very rare inherited metabolic disorder resulting due to the deficient function of the enzyme uroporphyrinogen III synthase (UROS), the fourth enzyme in the heme biosynthetic pathway. It is characterized by skin photosensitivity that may lead to scarring, blistering and increased hair growth at the face and back of the hands. Photosensitivity and infections can sometimes cause the loss of fingers and facial features.

**Hepatoerythropoietic porphyria (HEP)**

It is an extremely rare genetic disorder characterized by the deficiency of the enzyme uroporphyrinogen decarboxylase. This deficiency is caused due to the mutations of both copies of person's UROD gene. It is an autosomal recessive trait. The manifestations include blistering skin lesions, hypertrichosis and scarring over the affected skin areas. These manifestations appear during infancy or childhood and with similar frequency in males and females.[12]

**C. Mixed porphyrias**

This type of porphyria leads to symptoms of both acute and cutaneous porphyrias. They can therefore cause abdominal pain, can affect the skin and nervous system and may also cause psychiatric problems in some cases. The mixed porphyrias include Porphyria variegate (PV) and Hereditary coproporphyria (HCP).

**Porphyria variegate (PV)**

It is a hepatic form of porphyria. Protoporphyrinogen and coproporphyrinogen gets accumulated in the liver and gets oxidised to protoporphyrin and coproporphyrin, which are then transported in to the blood plasma and causes photosensitivity of the skin to the sunlight. It is an inherited disorder of the porphyrin-heme metabolism. Variegate porphyria is both a cutaneous porphyria with chronic blistering lesions on skin and an acute porphyria with severe neurovisceral symptoms.

**Hereditary coproporphyria (HCP)**

It is a rare metabolic disorder characterized by the deficiency of the enzyme coproporphyrinogen oxidase. This leads to the accumulation of porphyrin precursors in the body. It is caused due to the mutation in the gene CPOX. Inheritance is autosomal dominant but sometimes autosomal recessive. Most persons with this disorder remain asymptomatic. Attacks can be triggered due to certain chemicals including medications, fasting state, etc. However, it is characterized by neurovisceral symptoms and chronic blistering of skin lesions.[13]

**Treatment**

The first measure to be taken in the management of acute attacks is to avoid the precipitating factor. The main precipitating factors for acute porphyria includes excessive alcohol consumption, starvation, certain drugs, stressful conditions and abnormal regulation of sexual hormones. Before the application of any drug to a porphyria patient, make sure that the drug is safe in acute porphyria. The only exception for this is in the case of acutely life-threatening situation where any life saving drug can be given. The severe abdominal pain in acute attacks necessitates the need of analgesics. The frequently reported symptom of hyponatremia and hypomagnesemia should be corrected parenterally. If a patient is suffering from early or mild symptoms of an acute attack, advise the patient to consume increased amounts of carbohydrates(200-500g/day). If inappetite or nausea prevents the consumption of food, patient may change to fluids which should be enriched with glucose. If an attack progress with prolonged vomiting and severe abdominal pain, 24-h hospitalization is required with intravenous glucose(200-500g/24h) has been recommended. But practically, glucose is ineffective in hospitalized patients. So, we administer heme 3-5mg/kg in a short infusion once a day for 3-5 days with additional intravenous glucose.[14]

Any newly diagnosed individual with acute porphyria should be advised strictly to avoid the precipitating agents. Counselling of the patients is very important in terms of secondary prevention of further attacks. Family screening and counselling of affected family members is recommended.[15]

In case of porphyria due to the photosensitivity of the skin due to sun exposure, advise the patient to avoid sunlight as much as possible. Physical barriers like hats, gloves, long shirts or trousers and staying indoors is most effective. Skin ointments act as a protective at 404nm (visible) light. Iron removal by phlebotomy helps in reducing photosensitivity of the skin to sun exposure. Patients should be informed that porphyria can reappear, so periodic phlebotomy is essential. If no signs of increased iron body load is present in a patient with iron-deficit anaemia, low dose chloroquine or hydroxychloroquine can be effective.[16]

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