SYSTEMATIC REVIEW OF PORPHYRIA

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ABSTRACT

The porphyrias are a group of rare diseases in which chemical substances called porphyrins accumulate with high metabolism. The body requires porphyrins to produce heme, which carries oxygen in the blood. 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. This manifests with neurological symptoms or skin problems, or both. Porphyrias are classified in two ways, by symptoms and by pathophysiology. Symptomatically, acute porphryias cause brain and nerve involvement, often with severe abdominal pain, vomiting, neuropathy, and mental disturbances. Coetaneous porphyrrias cause skin problems, often exposure to sunlight, because porphyries react with light. Physiologically, porphyrias are classified as hepatic or erythropoietic based on the sites of accumulation of heme precursors, either in the liver or in the bone marrow and red blood cells. Administer the hematin infusions to treat the acute attacks in patients with the acute hepatic porphyrias, and perform the bone marrow or hematopoietic stem cell transplants therapies for congenital erythropoietic protoporphyria. These developments are reviewed to update the latest advances in these diverse disorders.

KEYWORDS: Porphyria, Coetaneous porphyrias, erythropoietic porphyrias.

INTRODUCTION

The porphyrias are a group of rare diseases in which chemical substances called porphyrins accumulate with high metabolism. The body requires porphyrins to produce heme, which carries oxygen in the blood. 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. This manifests with
neurological symptoms or skin problems, or occasionally both. Porphyrias are classified in two ways, by symptoms and by pathophysiology. Symptomatically, acute porphriyas cause brain and nerve involvement, often with severe abdominal pain, vomiting, neuropathy, and mental disturbances. Coetaneous porphyrias cause skin problems, often exposure to sunlight, because porphyries react with light. Physiologically, porphyrias are classified as hepatic or erythropoietic based on the sites of accumulation of heme precursors, either in the liver or in the bone marrow and red blood cells.\[1\]

The term porphyria is derived from the Greek πορφύρα, porphyra, meaning "purple pigment." a reference to the color of the porphyrins. Although original descriptions are attributed to Hippocrates, the disease was first explained biochemically by Felix Hoppe-Seyler in 1871, and acute porphyrias were described by the Dutch physician Barend Stokvis in 1889.\[2\]

**EPIDEMIOLOGY**

The combined prevalence of the acute porphyrias is approximately 5 cases per 100,000 persons. Porphyria cutanea tarda is the most common porphyria, with a prevalence of 1 in 10,000. The most common acute porphyria, acute intermittent porphyria, has a prevalence of approximately 1 in 20,000, and the prevalence of the most common erythropoietic porphyria, is estimated at 1 in 50,000 to 75,000. Congenital erythropoietic porphyria is extremely rare, with an estimated prevalence of 1 in 1,000,000 or less. Fewer than 200 cases have been reported in the literature.\[3\]

**CLASSIFICATION**

- Doss porphyria
- Acute intermittent porphyria
- Hereditary coproporphyria
- Variegate porphyria
- Erythropoietic porphyria
- Porphyria cutanea tarda
- Congenital erythropoietic porphyria
- x-linked dominant protoporphyria

**Symptoms:** Clinical manifestations depend on the type of porphyria.

**Doss Porphyria:** Doss porphyria, also known as plumboporphryia (ALA dehydratase deficiency), is extremely rare. Urinary ALA and coproporphyrin are markedly increased. In
some patients, the development of the acute porphyria syndrome while the patient received pharmacologic doses of erythropoietin, which resolved when the drug was stopped, suggests that by stimulating heme synthesis, clinical manifestation includes

- Abdominal pain
- Polyneuropathy.\textsuperscript{[4,5]}

**ACUTE INTERMITTENT PORPHYRIA**

Acute porphyria attacks are brought about by uncontrolled upregulation of the ALA synthase enzyme. This can be precipitated by certain lipophilic drugs, hypoglycemia ("the glucose effect") and a deficiency of heme,\textsuperscript{[6]} the end-product of the heme pathway that acts as a negative feedback mechanism in normal circumstances, symptoms are

- Severe abdominal pain
- Swelling of the abdomen (abdominal distention)
- Pain in your chest, legs or back.\textsuperscript{[7, 8, 9, 10]}

**HEREDITARY COPROPORPHYRIA**

Hereditary coproporphyria results in most cases from half-normal activity (50%) of coproporphyrin oxidase.\textsuperscript{[11]} The disease is an acute hepatic porphyria that is characterized by

- Abdominal pain
- Neuropsychiatric symptoms
- Cutaneous photosensitivity.\textsuperscript{[12, 13]}

**VARIEGATE PORPHYRIA**

Variegate porphyria is an autosomal dominant inherited trait that results in decreased activity of protoporphyrinogen oxidase. It is characterized clinically by photosensitive skin disease and a propensity to acute neurovisceral crises. It presents with

- Chronic blistering skin lesions.\textsuperscript{[14, 15]}

**ERYTHROPOIETIC PORPHYRIA**

![Figure No: 1](image)
In erythropoietic porphyria, the protoporphyrin molecule accumulates and can be excited by absorbing light energy. This causes the generation of free radicals and, thereby, photosensitivity of all tissues exposed to light. In the dark, several other toxic mechanisms have been described: deposition of protoporphyrin crystals in hepatocytes and bile canaliculi, interference with redox systems and, recently, formation of cytotoxic bile. Clinical manifestations of erythropoietic porphyria are

- Photosensitivity
- Insignificant hematologic abnormalities
- Liver disease.\(^{[16]}\)

**The hepatic manifestations of the disease are diverse**

- mildly disturbed liver enzymes \(^{[17]}\)

**PORPHYRIA CUTAEA TARDA**

Porphyria cutanea tarda (PCT) is characterized by the defective uroporphyrinogen III decarboxylase enzyme. There are 3 types of porphyria cutanea tarda with typical skin manifestations; patients present with.

- skin fragility
- erosions
- vesicles
- bullae
- milia in sun-exposed areas
- periorbital mottled hyperpigmentation
- hypertrichosis
- sclerodermoid changes
- ulceration.\(^{[18]}\)

![Figure No: 2](image-url)
CONGENITAL ERYTHROPOIETIC PORPHYRIA
Congenital erythropoietic porphyria, or Gunther's disease, is one of the least common porphyrias. It results from a deficient activity of uroporphyrinogen III synthase (URO-synthase). Hemolysis may be a feature in homozygous cases. Prolonged exposure to sunlight may precipitate,
- Blistering
- Rash
- red urine
- even blindness.\(^{[19, 20]}\)

X-LINKED DOMINANT PROTOPORPHYRIA
First described in 2008, this subtype is similar in presentation to erythropoietic protoporphyria but has a higher incidence of liver disease and higher levels of erythrocyte protoporphyrin, with an X-linked dominant inheritance pattern.\(^{[21]}\)

ETIOLOGY
Acute porphyria can be triggered by a number of drugs, most of which are believed to trigger it by interacting with enzymes in the liver which are made with heme. Such drugs include
- Sulfonamides, including sulfadiazine, sulfasalazine and trimethoprim/sulfamethoxazole.
- Sulfonylureas like glibenclamide, gliclazide and glimepiride, although glipizide is thought to be safe.
- Barbiturates including thiopental, phenobarbital, primidone, etc.
- Systemic treatment with antifungals including fluconazole, griseofulvin, ketoconazole and voriconazole. (Topical use of these agents is thought to be safe due to minimal systemic absorption.)
- Some anaesthetics like ketamine and etomidate.
- Certain Antibiotics like rifapentine, rifampicin, rifabutine, nitrofurantoin and possibly, metronidazole.\(^{[22]}\)

Genetics
Most forms of porphyria are inherited. Porphyria can occur if you inherit
- A defective gene from one of your parents (autosomal dominant pattern)
- Defective genes from both parents (autosomal recessive pattern)
Just because you have inherited a gene or genes that can cause porphyria doesn't mean that you'll have signs and symptoms. You might have what's called latent porphyria, and never have symptoms. This is the case for most carriers of the abnormal genes.\textsuperscript{[23]}

**DIAGNOSIS**

The differential diagnosis in porphyria includes the following

- Acute abdomen
- Hereditary tyrosinemia type I.\textsuperscript{[24]}
- Lead poisoning
- Pseudoporphyria is a bullous photosensitivity that most commonly arises as an adverse effect of a variety of medications, such as the antifungal voriconazole.\textsuperscript{[25]}

**Diagnostic considerations:** The clinical criteria of an acute attack of intermittent porphyria include the paroxysmal nature of the episode, the absence of other obvious causes, and the combination of various signs and symptoms, such as the following.\textsuperscript{[26]}

- Abdominal pain
- Autonomic dysfunction
- Hyponatremia
- Muscle weakness
- Psychiatric symptoms.\textsuperscript{[27]}

**LABORATORY INVESTIGATIONS**

- **Urine test:** If you have a form of acute porphyria a urine test may reveal levels of two substances: porphobilinogen and delta–aminolevulinic acid as well as other porphyrins.
- **Blood test:** If you have a form of cutaneous porphyria a blood test may show an elevation in the levels of porphyrins in your blood plasma.
- **A tool sample test:** Analysis of a stool sample may reveal elevated levels of one porphyrins that may not be detected in urine samples. this test may help your doctor determine your specific type of porphyria.
- **Imaging:** Computed tomography (CT) scanning of the abdomen and pelvis, magnetic resonance imaging (MRI)\textsuperscript{[28,29,30]}

**TREATMENT**

Acute porphyrias

- Treat pain with parenteral narcotics; complicated and debilitating chronic cases may require celiac plexus injection.\textsuperscript{[31]}
- Administer phenothiazines for manifestations such as nausea, vomiting, agitation; ondansetron or related drugs can also be used for nausea.
- Treat tachycardia and/or hypertension with propranolol or nadolol, which can be safely used for beta blockade once dehydration is ruled out.
- Promptly start glucose infusion in the form of 10% dextrose. At least 300-400 g should be given in 24 hours. The infusion is a time-buying measure to bridge the patient to more definitive treatment with hemin; by itself, glucose infusion is only effective for mild symptoms.[32]

- Treat acute porphyria attacks with hemin (plasma-derived intravenous heme); 1-4 mg/kg/d for up to 14 days is the definitive treatment and mainstay of management. Both heme arginate and heme hydroxide have been used. Thrombophlebitis is the major adverse effect. At least two thirds of patients have a good response, with resolution of pain and neurologic deficits.[33,34]
- Hemodialysis has been used in dire circumstances with some benefit when hemin was not available. Gonadotropin-releasing hormone (GdRH) analogues have been reportedly effective in some cases of acute intermittent porphyria, but these agents are not widely used.[35]
- Magnesium sulfate has been used to control seizures, as many regular antiseizure medications are contraindicated.

**Cutaneous porphyrias**

Treatment of cutaneous porphyrias focuses on reducing exposure to sunlight and the amount of porphyrins in your body to help eliminate your symptoms. This may include:

- **Drawing blood (phlebotomy):** Drawing a certain amount of blood from one of your veins reduces the iron in your body, which decreases porphyrins. You may need to have a phlebotomy repeated at regular intervals before cutaneous porphyria goes into remission.
- **Medication:** Drugs used to treat malaria — hydroxychloroquine (Plaquenil) or, less often, chloroquine (Aralen) — can absorb excess porphyrins and help your body get rid of them more quickly than usual. These medications are generally used only in people who can't tolerate a phlebotomy.
- **Beta carotene:** Long-term treatment of cutaneous porphyrias may include daily doses of prescription beta carotene. Beta carotene may increase your skin's tolerance to sunlight.
Your doctor can tell you what kind of beta carotene will work best for porphyria photosensitivity.

- Reducing or eliminating triggers: Triggers, such as certain medications or too much sunlight, which activated the disease, should be reduced or removed if possible, with guidance from your doctor.
- Vitamin D: Supplements may be recommended to replace vitamin D deficiency caused by avoidance of sunlight.

Non-pharmacological treatment

- Avoid medications known to trigger acute attacks. Ask your doctor for a list of safe and unsafe drugs.
- Don't use alcohol or illegal drugs.
- Avoid fasting and dieting that involves severe calorie restriction.
- Don't smoke.
- Minimize sun exposure. When you're outdoors, wear protective clothing and use a broad-spectrum sunscreen with a high sun protection factor (SPF).
- Treat infections and other illnesses promptly.
- Take steps to reduce emotional stress

Future Therapies

Bone-marrow transplantation presents its own challenges, and is considered a last resort. In the longer term, hope to cure porphyria is invested in gene therapy, in which the faulty genes are replaced with functional ones using a virus as a vector (delivery method). The technique has been shown to be effective in cell culture, but there is still a long way to go before gene therapy for CEP can be used in clinical practice.

Other future treatments for porphyria will depend on the results obtained from research with experimental animal--and even plant--models. Some of these are improbable, to say the least. For example, all fox squirrels (Sciurus niger) have a gene defect that gives them a form of CEP, yet they do not suffer any adverse consequences, for unknown reasons. Studies of the animals could yield clues that would be useful in fighting CEP.

Surprisingly, even plants--which use the green porphyrin, chlorophyll, to absorb light energy--can suffer from a condition analogous to porphyria. Plants make chlorophyll via a pathway very similar to that for heme production in animals. Mutations in the gene for the final step in
this pathway lead to a buildup of porphyrins in the leaves. On exposure to sunlight the leaves blister, and eventually wither and die. The process is so similar to human porphyria that some researchers hope to find a cure for the human condition by studying the properties of so-called "vampire plants," like maize.\[36\]

**CONCLUSION**

The porphyrias, are a diverse group of metabolic disorders that often are diagnosed and treated by hematologists. Recent advances in our understanding of these disorders include the recognition of their genetic heterogeneity and disease variants, improved molecular diagnostics, genotype/phenotype correlations, and current and experimental treatments. Current research is focused on developing gene and stem cell replacement, pharmacologic chaperones to rescue misfolded mutant enzymes, and future efforts to correct specific mutations in induced pluripotent stem cells from porphyria patients followed by transplantation of hepatic or erythroid From.

**REFERENCES**

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