Understanding PORPHYRIA

An Overview of the Porphyrias

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UNITED PORPHYRIAS ASSOCIATION
Advancing Awareness, Research & Therapies

What is PORPHYRIA?

Porphyria is not a single disease - but rather a group of eight disorders. They each stem from defects in the synthesis of heme and its biochemical precursors. As a result of recent genetic studies and careful clinical assessments [genotype-phenotype correlations], it is now known that most people with potentially disease-associated genetic mutations for some of the types of porphyria never develop clinical symptoms or signs of disease.

In biochemically active porphyria, there is accumulation in the body of excess porphyrins or porphyrin precursors. Although these are normal body chemicals, they normally do not accumulate to the high levels that cause clinical disease as occurs in biochemically and clinically active porphyria.

Precisely which of these chemicals builds up depends upon the type of porphyria. The clinical manifestations of the different types of porphyria are not the same. Forms of treatment also depend on the type of porphyria. Therefore, it is difficult to make general statements that apply to all these disorders.

The symptoms and signs of the porphyrias arise mostly from effects of heme precursors on the nervous system or the skin. Effects on the nervous system occur in **acute hepatic porphyrias**. Proper diagnosis is often delayed because the symptoms are nonspecific.

Skin manifestations occur in the **cutaneous porphyrias** and may include burning, tingling, itching, and eventual swelling, and pain [in erythropoietic protoporphyria and X-linked protoporphyria] or blistering and bullae formation, resulting in sores that are slow to heal, often become secondarily infected, and eventually lead to scarring and thickening of sun-exposed areas of the skin, especially the backs of the hands and forearms.

TWO MAIN CATEGORIES

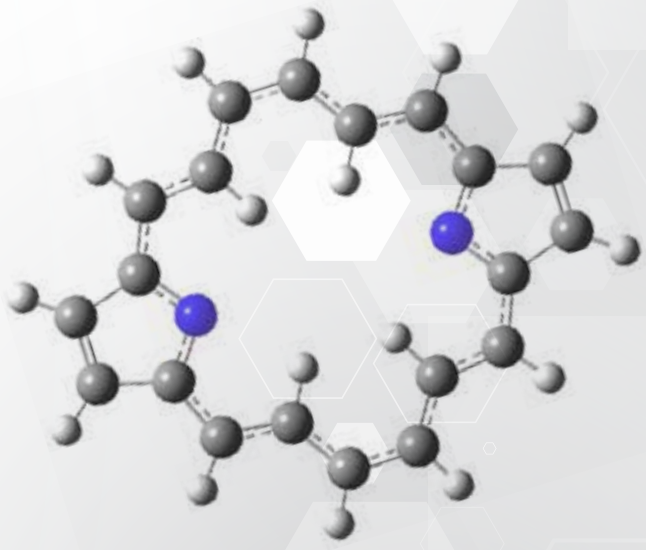
ACUTE HEPATIC PORPHYRIA

Affects the nervous system; proper diagnosis is often delayed because the symptoms are nonspecific.

CUTANEOUS PORPHYRIA

Skin manifestations include burning, tingling, itching, swelling, pain or blistering and bullae formation that often results in sores, infections and scarring.

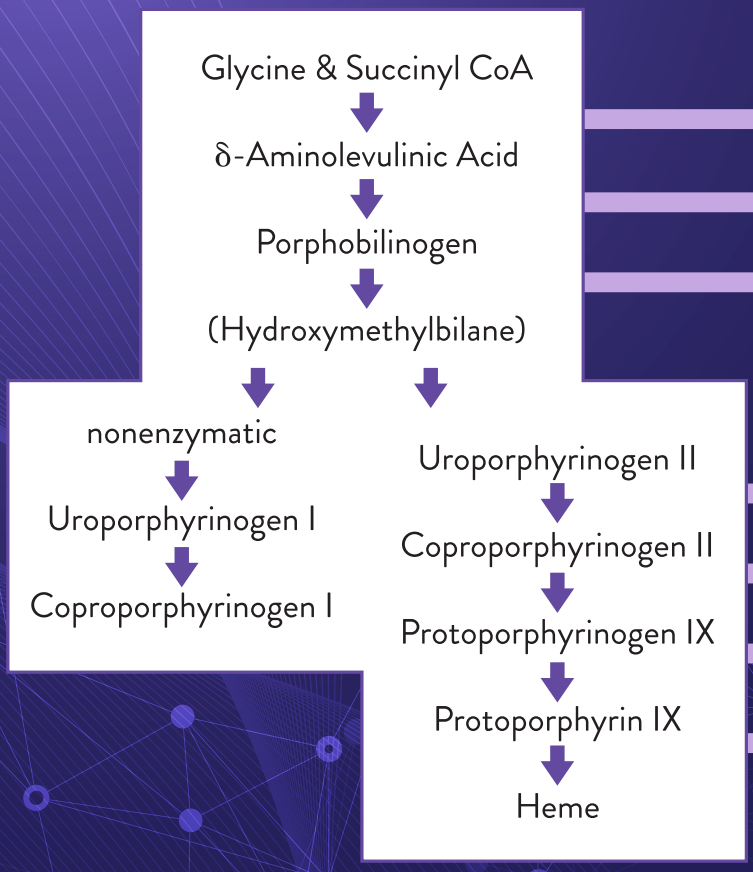
The terms “porphyrin” and “porphyria” are derived from the Greek word “porphyrus,” which means purple. Urine from some porphyria patients may be pink to purple in color due to the presence of excess porphyrins and related substances in the urine, and, in some, the urine may darken after exposure to air [oxygen] and light.



How are the Porphyrias CLASSIFIED?

The best way to classify a case of porphyria is to determine which enzyme is deficient. The enzymes that are deficient in the porphyrias normally act in sequence to make heme from simpler molecules. Heme is a vital substance for all body organs and consists of an iron atom in the center of a protoporphyrin molecule. The sequence of enzymes and intermediates in the pathway to produce heme is shown below in the diagram.

As shown, each of the eight types of porphyria is associated with an abnormality (usually a deficiency) of one of these enzymes. Sometimes, other classifications are useful. For example, each porphyria is either "hepatic", in which accumulation of pathway intermediates occurs foremost in the liver, or "erythropoietic", in which such accumulation occurs foremost in the bone marrow. Porphyrias with skin manifestations are called "cutaneous porphyrias." The "acute porphyrias" are those characterized by attacks of pain and other neurological manifestations. They are also known as "acute hepatic porphyrias". Their symptoms can be both rapidly appearing (i.e., acute) and severe. An individual may be considered "latent" if he or she has the required enzyme deficiency but has never developed symptoms.



ENZYME	DISEASE
δ-Aminolevulinic Acid Synthase	X-linked protoporphyria
δ-Aminolevulinic Acid Dehydtratase	ALAD Porphyria
Porphobilinogen Deaminase	Acute Intermittent Porphyria
Uroporphyrinogen III Cosynthase	Congenital Erythropoietic Porphyria
Uroporphyrinogen Decarboxylase	Porphyria Cutanea Tarda, Hepatoerythropoietic Porphyria
Coproporphyrinogen III Oxidase	Hereditary Coproporphyria
Protoporphyrinogen Oxidase	Variegate Porphyria
Ferrochelatase	Erythropoietic Protoporphyria

Types of PORPHYRIA

ACUTE HEPATIC PORPHYRIAS (AHPs)

There are four inherited disorders that have similar disease manifestations, namely, recurrent acute attacks, characterized by generalized severe abdominal pain and variably with additional features. The names of these four diseases are:

- Acute porphyria due to severe deficiency of ALA dehydratase [ADP]
- Acute intermittent porphyria [AIP]
- Hereditary coproporphyria [HCP]
- Variegate porphyria [VP]

In all, the biochemical hallmark of acute attacks is marked up-regulation of hepatic ALA synthase-1, the first and normally rate-controlling enzyme of hepatic heme biosynthesis, which, coupled with distal defects in other enzymes in the pathway, leads to marked overproduction of ALA and PBG. It is likely that ALA is the most important neurotoxin that gives rise to most of the clinical features of the acute attacks, as well as to the long-term complications of these disease, such as increased risks of kidney and liver disease and of hepatocellular carcinoma. Down-regulation of ALA synthase-1 by hemin or by givosiran is the treatment of choice for management of the symptomatic acute porphyrias.

EXTREMELY RARE

ALAD PORPHYRIA (ADP)

This form of porphyria is inherited as an autosomal recessive trait and is extremely rare. The symptoms are very similar to those of acute intermittent porphyria.

Deficient Enzyme:	Delta-Aminolevulic Acid Dehydratase (ALAD)
Substrate:	Delta aminolevulinic acid (ALA)
Product:	Porphobilinogen (PBG)
Biochemical Finding:	A substantial increase in urinary ALA with normal or slight increase in PBG and a substantial increase in urinary porphyrins with a predominance of coproporphyrin III AND a substantial increase in erythrocyte zinc protoporphyrin; negative testing for heavy metal (especially lead) poisoning and hereditary tyrosinemia
Molecular/ Genetic Findings & Inheritance:	Two disease causing ALAD mutations, leading to severe deficiency in activity of the enzyme [< 10% of normal]) —autosomal recessive

There is a severe deficiency (less than 10% of normal) of the enzyme ð-aminolevulinic acid dehydratase (ALAD) and increased excretion of ð-aminolevulinic acid (ALA) in the urine. Coproporphyrin in urine and zinc protoporphyrin in red blood cells are also increased. However, unlike all the other forms of acute hepatic porphyrias, in ADP urinary PBG excretions are normal. IV heme treatment has been effective in managing recurrent acute attacks of ADP.

ACUTE INTERMITTENT PORPHYRIA (AIP)

Deficient Enzyme:	Porphobilinogen Deaminase (PBGD), aka hydroxymethylbilane synthase (HMBS)
Substrate:	Porphobilinogen
Product:	Hydroxymethylbilane
Biochemical Finding:	Most with disease-causing mutations have no symptoms or biochemical abnormalities most of the time. Those with abnormalities exhibit a variable increase in urinary and/or serum PBG, ALA, and porphyrins
Molecular/ Genetic Findings & Inheritance:	A disease -causing mutation in the PBGD (HMBS) gene, leading to ~ 50% decrease in activity of the enzyme particularly in the liver — autosomal dominant

This is the most common of the acute hepatic porphyrias. Its inheritance is autosomal dominant. The deficient enzyme is porphobilinogen deaminase (PBGD), also known as hydroxymethylbilane synthase (HMBS). A deficiency of PBGD is not sufficient by itself to cause symptoms in AIP, and other inciting factors must also be present. These include hormones, drugs, and dietary changes. Sometimes, inciting factors cannot be identified. An ongoing challenge is to identify additional genetic traits or other environmental factors that trigger clinical disease in people with inherited deficiency of PBGD.

SYMPTOMS

Most individuals who have inherited the gene for this type of porphyria lead normal lives. In the minority who suffer from the disease, the symptoms usually appear only after puberty, and are much more frequent in women than in men, emphasizing the important role of female sex hormones, especially progesterone, in leading to active clinical disease. Acute attacks develop over several hours or days. Abdominal pain, which can be severe, and which lasts for hours to days, is the most common symptom. Insomnia and anxiety are common early symptoms. When attacks are more severe, nausea and vomiting often occur and are associated with the inability to eat, leading to negative energy balance, which exacerbates the acute attacks. Most patients with acute attacks develop constipation, and pain in the back, arms and legs, muscle weakness (due to effects on nerves supplying the muscles), urinary retention, palpitations (due to a rapid heart rate and often accompanied by increased blood pressure), anxiety, agitation, confusion, hallucinations, and seizures may also occur.

Sometimes the levels of salt (sodium and chloride) in the blood decrease markedly [hyponatremia] and contribute to some of these symptoms. The liver and kidneys may be damaged over time, and the risk of developing liver cancer is increased, especially after age 50. The skin is not affected, except in some patients who have developed severe kidney disease.

DIAGNOSIS

This rare disease can mimic a host of other more common conditions, so its presence is often not suspected. It can be readily diagnosed by measuring urine porphobilinogen (PBG) and creatinine in a single random urine sample. During acute attacks, levels of urinary PBG/creatinine are increased 5 or more times the upper limit of normal. The increases are often much higher, 20-50-times the upper limit of normal.

Too often, however, only urinary porphyrins are measured, rather than PBG. Urinary porphyrin levels may be increased for lots of reasons other than porphyrias. The elevated values may be misinterpreted as evidence for acute porphyria. The finding of markedly increased levels of PBG in urine [more than 5 times the upper limit of normal] establishes that the patient has one of the acute porphyrias. The exact type is determined by follow-up testing of plasma and fecal porphyrins. Testing for PBGD deficiency in red blood cells is also available and can be helpful in making a preliminary diagnosis.

DNA testing should be done to confirm the diagnosis of AIP, or any other type of porphyria. Many different mutations have been identified in different AIP families. But within one family, those members with deficiency of PBGD will have the same mutation. Once the familial mutation is known, DNA testing of relatives will identify others who have the mutation with a very high degree of accuracy. This approach is now preferred to measuring PBGD enzyme activity in red blood cells because some patients with AIP have entirely normal PBGD activities in red blood cells, whereas many more have activities in a low normal range that overlaps with persons without porphyria.

TREATMENT & PROGNOSIS

Hospitalization is often necessary for acute attacks. Medications for pain, nausea, and vomiting, as well as close observation for metabolic and neurological complications are generally required.

A high intake of glucose or other carbohydrates can help suppress disease activity and can be given by vein or by mouth. Glucose and intravenous hemin are the only available specific treatments for acute attacks. Hemin is more effective and should be started soon after diagnosis of an attack. It is not advisable to delay heme therapy until glucose alone is found to be ineffective. Hemin is available as Panhematin® (Recordati Rare Diseases) in the United States. To order call 1-800-746-6273 (24hrs/7 days a week). Healthcare professionals can contact Recordati at 1-888-575-8344.

Heme arginate (Normosang™, Orphan Europe) is another preparation of hemin for intravenous administration and is available in Europe and some other countries. Panhematin® is given by slow infusion into a large vein or central catheter. Use of a small vein in the hand or arm carries the risk of painful irritation (phlebitis) and potentially destruction of the vein. The risk of this complication is reduced by reconstituting the Panhematin® powder with a solution of human albumin rather than water. (Directions for preparing Panhematin® in this manner can be obtained from porphyria specialists.) Hemin is also given to prevent attacks in selected patients with recurrent bouts of symptoms (off-label use).

During treatment of an attack, attention should be given to salt and water balance. Harmful drugs should be stopped. Attacks may be precipitated by low intake of carbohydrates and calories in an attempt to lose weight. Thus, adequate nutrition and dietary counseling are very important (see below). Premenstrual attacks often resolve quickly with the onset of menses. AIP is particularly dangerous if the diagnosis has not been made and if harmful drugs are continued or started during attacks, for example use of barbiturates or phenytoin (Dilantin) for treatment of seizures.

The prognosis is usually good if the disease is recognized and if treatment and preventive measures are started before severe nerve damage has occurred. Nerve damage and associated muscle weakness can improve over a period of months or longer after a severe attack. Mental symptoms may occur during attacks but are usually not chronic. Some patients develop chronic pain after experiencing many attacks. Wearing a MedicAlert® bracelet is advisable for patients who have had attacks, but medical providers should keep in mind that new symptoms may not always be due to porphyria.

Another way to prevent recurrent attacks of AIP or other acute hepatic porphyrias [AHP], is to administer givosiran [Givlaari, Alnylam Pharma]. This is a small inhibitory RNA that is targeted specifically to hepatocytes [liver cells] and that down-regulates the over-expression of ALA synthase-1, the first and normally rate-controlling enzyme in the heme synthetic pathway. Regardless of the type of AHP, marked up-regulation of hepatic ALA synthase-1 is the key abnormality that leads to overproduction of ALA and PBG and to the symptoms and signs of porphyric attacks. In patients with histories of frequent attacks, givosiran proved to be markedly effective in decreasing further attacks and generally to be well-tolerated. Givosiran has been approved for use in adults with AHP in the USA and in children older than 12 years and adults in the European Union.

DIET

AIP patients should maintain a balanced diet with protein, fat and 60% carbohydrate. If weight loss is desired, the recommended method is calorie restriction that will cause loss of 1-2 lbs. per week. Drastic remedies (starvation, highly restricted diets, gastric bypass surgery, etc.) increase the risk of a porphyria attack and are not recommended. It is advisable at the start to consult a dietitian for an estimate of normal caloric intake, which varies from one person to another, and design of a diet that will reduce daily calories by approximately 10% and lead to gradual weight loss. Pregnancy is generally well tolerated, although some women experience attacks during pregnancy or in the post-partum period that require treatment with hemin or givosiran.

HAVING CHILDREN

Offspring of a parent with AIP have a 50% chance of inheriting the gene for AIP, but pre-natal genetic testing of fetal cells is not recommended, because the results are not relevant to management during pregnancy or for the infant. Unlike some other porphyrias (CEP, EPP), in AIP there is no evidence that disease severity is related to specific mutations. In family studies, only 5-10% of AIP carriers will have symptoms regardless of the mutation that is present. As a child approaches puberty, DNA testing for the family mutation should be performed, so that the child, if found also to be a carrier of the mutation, can be advised of measures to minimize the risk of an acute attack. With this, most will enjoy a life without symptoms of porphyria.

HEREDITARY COPROPORPHYRIA (HCP)

This is one of the acute hepatic porphyrias and is similar to AIP. Blistering skin photosensitivity develops in some patients, resembling PCT, but is much less common than in VP. The deficient enzyme is coproporphyrinogen oxidase [CPOX].

The diagnosis is established by finding excess coproporphyrin (especially coproporphyrin type III) in urine and stool. Urinary ALA and PBG are increased during acute attacks but become normal on recovery more commonly and quickly than in AIP. Reliable assays for the deficient enzyme are not generally available. The enzyme is found in mitochondria, which are not present in red blood cells. Precautions and treatment for acute attacks are as described for AIP.

Deficient Enzyme:	Coproporphyrinogen Oxidase (CPOX)
Substrate:	Coproporphyrinogen III
Product:	Protoporphyrinogen IX
Biochemical Finding:	Patients with HCP may have only elevated fecal and urinary concentrations of coproporphyrin III. During heightened biochemical and clinical activity some also show an increase in urinary or serum PBG and ALA.
Molecular/ Genetic Findings & Inheritance:	A disease-causing mutation in CPOX, leading to ~ 50% of normal activity of the enzyme — autosomal dominant

VARIEGATE PORPHYRIA (VP)

This form of hepatic porphyria is most common in the South African white population of Dutch descent. It is less frequent elsewhere. It is an autosomal dominant disorder and may produce acute attacks (as in AIP) as well as chronic, blistering skin photosensitivity. The deficient enzyme is protoporphyrinogen oxidase [PPOX].

The diagnosis is made by finding excess coproporphyrin in urine and both coproporphyrin and protoporphyrin in feces. The most sensitive biochemical screening test for VP is a plasma porphyrin fluorescence assay that measures the wavelength of the light emitted after excitation by blue light [410 nm]. Peak emission at 626 nm occurs only in VP. In patients with skin manifestations, it is important to distinguish VP or HCP from PCT, because treatment by phlebotomy or low-dose hydroxychloroquine is very successful in PCT but not VP and HCP. Acute attacks are managed and may be prevented as in AIP.

Deficient Enzyme:	Protoporphyrinogen Oxidase (PPOX) Coproporphyrinogen III
Substrate:	Protoporphyrinogen IX
Product:	Protoporphyrin IX
Biochemical Finding:	Patients with VP may show increases in urinary coproporphyrinogen III and fecal coproporphyrin III and protoporphyrin IX. During heightened biochemical and clinical activity some also show an increase in ALA and PBG in urine. A useful and simple test for VP is measurement of the fluorescence emission spectrum of plasma after excitation with light of 410 nm wavelength, with a peak at or near 626 nm being specific for VP.
Molecular/ Genetic Findings & Inheritance:	A disease-causing mutation in CPOX, leading to ~ 50% of normal activity of the enzyme — autosomal dominant

DRUGS SAFETY
& Acute Hepatic Porphyria

The following are partial lists of drugs that are probably safe or potentially dangerous in AHP. Recommendations about drugs for these porphyrias are based on experience with porphyria patients and by tests in experimental model systems. Sometimes the properties of a drug can provide clues about its safety in porphyria. Drugs that have not been tested or assessed by experts are best avoided if possible. If such a drug is given to a patient with known AHP, it is recommended that urine samples for ALA, PBG, porphyrins, and creatinine be collected prior to the first dose and again weekly for the first month of such therapy. In addition, patients taking such drugs should record with care any symptoms or other features that they think are likely related to drug use. Information about such experiences should be transmitted to the UPA at info@porphyria.org to be tracked as drug effects and experiences in AHP.

If a question of drug safety arises, The Drug Database for Acute Porphyria maintained by The European Porphyria Network (Epnet) www.drugs-porphyria.org should be consulted, and/or a physician with special knowledge about porphyrias should be contacted. A list of such physicians may be requested from the UPA.

Some drugs and chemicals regarded as generally **safe** for use in AHP:

- Acetaminophen
- Aspirin
- Atropine
- Beta blockers
- Bromides
- Cimetidine
- Cephalosporins
- Chloral hydrate
- Estrogens1,3
- Famotidine
- Glucocorticoids
- Insulin
- Levetiracetam
- Lisinopril
- Macrolide antibiotics
  - Azithromycin
  - Clarithromycin
  - Erythromycin
- Narcotic analgesics
- Penicillin and derivatives
- Phenothiazines
  - Prochlorperazine
  - Promethazine
- Serotonin reuptake inhibitors (anti-depressants)
- Streptomycin

Some drugs and chemicals regarded as potentially risky and **unsafe** in AHP:

- Alcohol in excess
- Many anti-convulsants (anti-epilepsy drugs)
- Barbiturates[1]
  - Carbamazepine
  - Hydantoins[1]
  - Valproic acid
- Birth control pills
  - but low-dose agents may help to decrease monthly attacks in some
- Calcium channel blockers[2]
  - Nifedipine
- Carbamazepine[1]
- Carisoprodol[1]
- Clonazepam
- Danazol[1]
- Diclofenac[1]
- Diones
  - Trimethadione
  - Paramethadione
- Elagolix
- Eslicarbamazepine
- Ergot preparations
- Ethchlorvynol[1]
- Felbamate
- Glutethimide[1]
- Griseofulvin[1]
- Mephenytoin
- Meprobamate[1]
- Methyprylon
- Metoclopramide[1]
- Primidone[1]
- Progesterone
- Progestins/ Synthetic
- Pyrazinamide[1]
- Pyrazolones
  - Aminopyrine
  - Antipyrine
- Rifampin1
- Rifapentine
- Succinimides
  - Ethosuximide
  - Methsuximide
- Sulfonamide antibiotics[1]
- Tramadol[2]
- Valproic acid[1]

1 Porphyria is listed as a contraindication, warning, precaution, or adverse effect in 1994 U.S. labeling for these drugs.

2 There is strong evidence in laboratory studies and some clinical evidence that these agents may be harmful.

3 There is little evidence that estrogens alone are harmful in acute porphyrias. They have been implicated as harmful based mostly on experience with estrogen/progestin combinations, and because they can exacerbate porphyria cutanea tarda. Some patients with AIP, HCP, VP, and ADP may tolerate a low dose estrogen patch.

4 Although porphyria is listed as a precaution in U.S. labeling for this drug, it is regarded as safe by other sources.

Extensive drug lists, which are actively curated and updated by Norwegian physicians with expertise, can be found at the Epnet site, **www.drugs-porphyrias.org**.

DRUG SAFETY DATABASE
www.drugs-porphyrias.org

CUTANEOUS PORPHYRIAS

The more common forms of cutaneous porphyrias are porphyria cutanea tarda [PCT] and erythropoietic protoporphyria [EPP]. Hepatoerythropoietic porphyria [HEP] is a severe homozygous or compound heterozygous form of inherited PCT that manifests in young children. X-linked protoporphyria [XLP] closely resembles EPP clinically but is due to a gain-of-function mutation in erythroid ALA synthase-2. Congenital erythropoietic uroporphyria is due to severe deficiency of uroporphyrinogen 3 synthase [UROS].

- Erythropoietic Protoporphyria (EPP)
- X-Linked Porphyria (XLP)
- Congenital Erythropoietic Porphyria (CEP)
- Hepatoerythropoietic Porphyria (HEP)
- Porphyria Cutanea Tarda (PCT)

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

Deficient Enzyme:	Ferrochelatase (FECH)
Substrate:	Protoporphyrin IX & divalent iron [Fe++]
Biochemical Finding:	A marked increase in erythrocyte protoporphyrin [PP] with a predominance of metal free protoporphyrin; also, increased plasma PP.
Molecular/ Genetic Findings & Inheritance:	A disease-causing FECH mutation in trans to the low expression FECH allele [IVS3 -48 T>C] OR two disease-causing FECH mutations — autosomal recessive

This porphyria is due to a deficiency of ferrochelatase [FECH], the final enzyme in the heme biosynthetic pathway. Inheritance is autosomal recessive.

Many different mutations of the ferrochelatase gene have been found in various EPP families. In most families, a severe ferrochelatase mutation inherited from one parent is paired in trans (on the other allele) with a genetic variant called IVS-3-48T>C inherited from the other parent. This variant, also described as “low expression” or “hypomorphic”, is common in Caucasians (about 10% of individuals carry it), is even more common in east Asians (~ 40%), and very rare in Africans. It has no consequences unless paired with a severe mutation.

In EPP, protoporphyrin accumulates in the bone marrow and then appears in red blood cells and blood plasma. Excess protoporphyrin is excreted by the liver into the bile, after which it enters the intestine and is excreted in the feces. Urinary porphyrins are normal. The diagnosis of EPP is established by finding increased protoporphyrin in red blood cells. When ferrochelatase is deficient, formation of both iron-protoporphyrin (heme) and zinc protoporphyrin is impaired. Thus, for diagnosis of EPP, it must be demonstrated that the excess protoporphyrin found in red blood cells is metal-free and not complexed with zinc.

SYMPTOMS

Photosensitivity is usually first noted in early childhood and persists throughout life. It is generally more severe in the spring and summer. Pain, burning, and itching, progressing to swelling and redness of the skin develop soon after exposure to sunlight, including sunlight that passes through window glass. Incandescent indoor lights and some types of fluorescent and LED lighting also may cause symptoms in some individuals. A severe sunlight reaction may take several days to subside, but seldom leaves significant scarring. Other manifestations may include gallstones containing protoporphyrin and, occasionally, severe liver damage. Iron deficiency with mild anemia is common in EPP, and the cause is not known at present.

DIAGNOSIS

The diagnosis of EPP is established by finding a high level of erythrocyte protoporphyrin and showing that the increased amount is almost all metal-free protoporphyrin rather than zinc protoporphyrin. It is important to choose a laboratory that does this properly (e.g., the Porphyria Laboratory at the University of Texas Medical Branch, and Mayo Medical Laboratories). The method used by Quest and LabCorp only measures zinc protoporphyrin, and ARUP does not separately measure metal-free and zinc protoporphyrin.

TREATMENT & PROGNOSIS

Systematic reviews and abundant patient accounts show that drugs such as β-carotene (Lumitene) or cysteine show no evidence of efficacy. Afamelanotide (Scenesse), an analogue of alpha-melanocyte stimulating hormone, administered as a subcutaneous biodegradable implant was FDA approved for the treatment of adults with EPP and XLP in 2019. Bitopertin, Dersimelagon (MT-7117) and Cimetidine are currently in clinical trials for EPP.

"Sunlight avoidance and protective clothing are recommended for the prevention of phototoxic symptoms in protoporphyria. Window tinting for cards can be useful. Because some patients report a small benefit with broad-spectrum and/or tinted sunscreens such as zinc oxide and titanium dioxide and because these agents block a portion of the far UVA wavelengths (350-399 mm) of light that activate protoporphyrin, it is reasonable for patients to use these agents for the prevention of phototoxic symptoms."[1]

"No studies evaluating treatments for phototoxicity have been done. Anecdotally, many patients choose to self-treat with ice, cold water, or cold compresses, resulting in minor relief, although others report that both cold and heat worsen symptoms."[1] Excess protoporphyrin in bile may form gallstones, which can become symptomatic at a young age (in teens or young adults), requiring a cholecystectomy. In a small number of cases, the crystal deposits obstruct bile flow, leading to progressive liver injury and need for liver transplantation. Liver damage may also improve with a combination of medical treatments.

Patients are advised to avoid drugs that impair bile flow (cholestasis), including estrogens and alcohol. Some patients with EPP report that drinking alcoholic beverages increases their photosensitivity. EPP patients should also be vaccinated against hepatitis A and B. Because patients with cutaneous porphyrias avoid sunlight, they are at increased risk for vitamin D deficiency and for bone thinning. Bone density and the level of 25-OH vitamin D in blood should be followed, with supplementation as needed.

Iron-deficiency anemia is common in EPP patients. Treatment with iron in EPP should be done with care and close observation, because it has led to worsening photosensitivity in some cases, especially those given large doses of iron intravenously.

Contact UPA for access to further expert guidance for issues related to anemia, liver function, vitamin D, anxiety and depression, pregnancy, etc.

1 Dickey, A. K., Naik, H., Keel, S. B., Levy, C., Beaven, S. W., Elmariah, S. B., Erwin, A. L., Goddu, R. J., Hedstrom, K., Leaf, R. K., Kazamel, M., Mazepa, M., Philpotts, L. L., Quigley, J., Raef, H., Rudnick, S. R., Saberi, B., Thapar, M., Ungar, J., Wang, B., ... Porphyrias Consortium of the Rare Diseases Clinical Research Network (2022). Evidence-based consensus guidelines for the diagnosis and management of erythropoietic protoporphyria and X-linked protoporphyria. Journal of the American Academy of Dermatology, S0190-9622(22)02611-1. Advance online publication. https://doi.org/10.1016/j.jaad.2022.08.036

X-LINKED PROTOPORPHYRIA (XLP)

In approximately 10% of patients with protoporphyria the disease results from a mutation of ALAS2 (∂-aminolevulinic acid synthase 2, the erythroid or bone marrow form of the first enzyme in the heme synthetic pathway) rather than ferrochelatase.

These are gain of function mutations, so ALAS2 is overactive and generates more pathway intermediates, including protoporphyrin, than required for heme and hemoglobin synthesis. Because the ALAS2 gene is found on the X chromosome, inheritance of this form of protoporphyria is X-linked. Men have one X chromosome, and those who inherit an ALAS2 gain of function mutation always develop protoporphyria. Women have two X chromosomes, one of which is variably inactivated, so, if they inherit a gain of function ALAS2 mutation, they may have severe or mild disease, or no disease.

Deficient Enzyme:	Delta Aminolevulinic Acid Synthase (ALAS)-2
Substrate:	Succinyl CoA and Glycine
Product:	delta-aminolevulinic acid [ALA]
Biochemical Finding:	A marked increase in erythrocyte protoporphyrin [PP] with a considerable percentage of metal-free protoporphyrin; also increased plasma PP.
Molecular/ Genetic Findings & Inheritance:	Genetic abnormality in the gene for ALAS2, usually a deletion in exon 11, leading to increased activity of the enzyme (gain of function mutation) — X-linked

DIAGNOSIS

Like EPP, XLP is diagnosed by finding a marked elevation in erythrocyte protoporphyrin. Because ferrochelatase is normal, formation of zinc protoporphyrin is not impaired, so there is a greater proportion of zinc protoporphyrin in XLP than in EPP, although metal-free protoporphyrin almost always predominates.

TREATMENT & PROGNOSIS

These are the same as in EPP. On average, porphyrin levels are higher and photosensitivity greater in XLP than in most patients with EPP. Treatment with iron is beneficial in XLP, leading to decrease in protoporphyrin overproduction and lessening of photosensitivity.

CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

This autosomal recessive disease (also known as Günther's disease) is extremely rare. The deficient enzyme is uroporphyrinogen III synthase (UROS).

Various mutations in the gene for this enzyme have been identified. As is characteristic of the erythropoietic porphyrias, symptoms begin during infancy. Sometimes, CEP is recognized as a cause of anemia in a fetus before birth. In less severe cases, symptoms may begin during adult life. Sometimes adult-onset cases are associated with expansion of a clone of cells in the bone marrow with mutated UROS. Porphyrins are markedly increased in bone marrow, red blood cells, plasma, urine, and feces in all cases of CEP. Porphyrins are deposited in the teeth and bones before birth.

Deficient Enzyme:	Uroporphyrinogen III Synthase (UROS), aka uroporphyrinogen III cosynthase
Substrate:	Hydroxymethylbilane
Product:	Uroporphyrinogen III
Biochemical Finding:	A marked increase in erythrocyte, urinary and plasma porphyrins with a predominance of uroporphyrin I and coproporphyrin I.
Molecular/ Genetic Findings & Inheritance:	Two disease-causing UROS mutations leading to severe deficiency in activity of the enzyme — autosomal recessive

SYMPTOMS

Skin photosensitivity may be extreme and lead to blistering, severe scarring, and increased hair growth. Bacteria may infect the damaged skin. Phototoxic damage and infection may destroy facial features and fingers. Therefore, avoiding sunlight is especially important in this porphyria. Red blood cells have a shortened life span, and this often results in anemia. Although UROS activity is markedly deficient, synthesis of heme and hemoglobin is increased to compensate for shortened red blood cell survival.

TREATMENT & PROGNOSIS

Blood transfusions and perhaps removing the spleen may reduce porphyrin production by the bone marrow. Removal of blood to produce iron deficiency has recently been found to be effective treatment of CEP. Bone marrow or human stem cell transplantation has been very effective and is the treatment of choice in severe childhood cases. Gene therapy or chaperone molecules that stabilize the residual UROS enzyme activity are being investigated and may be used in the future.

HEPATOERYTHROPOIETIC PORPHYRIA (HEP)

EXTREMELY RARE

This very rare type of porphyria results from inheritance of UROD mutations from both parents, causing a deficiency of UROD that is more severe than in PCT. The enzyme deficiency is inherited as an autosomal recessive trait.

The manifestations of HEP resemble CEP, with skin blistering usually beginning in infancy. Porphyrins are increased in red blood cells, in contrast to PCT, as well as liver, plasma, urine, and feces.

Deficient Enzyme:	Uroporphyrinogen Decarboxylase
Substrate:	Uroporphyrinogen III
Biochemical Finding:	A substantial increase in urinary, plasma and erythrocyte porphyrin with a predominance of Uroporphyrin and Heptacarboxyl porphyrin.
Molecular/ Genetic Findings & Inheritance:	Two disease-causing mutations in trans in UROD, leading to severe deficiency in activity of the enzyme from infancy — autosomal recessive.

PORPHYRIA CUTANEA TARDA (PCT)

This disease is the most common of the porphyrias and results from a deficiency of the enzyme, uroporphyrinogen decarboxylase (UROD).

The result is accumulation of porphyrins (mainly uroporphyrin) in the liver, blood, and skin. PCT is mainly an acquired disease, but some individuals have a genetic (autosomal dominant) deficiency of UROD that contributes to its development. These individuals are referred to as having "familial (type 2) PCT". Type 1 refers to the majority who do not have UROD mutations. In both types, the causation of disease is multi-factorial, meaning that its expression requires a combination of genetic or acquired or environmental factors, including alcohol, smoking, hepatitis C, HIV, increased body iron, and estrogens (used, for example, in oral contraceptives and for estrogen replacement after menopause).

Deficient Enzyme:	Uroporphyrinogen Decarboxylase (UROD)
Substrate:	Uroporphyrinogen III
Product:	Coproporphyrinogen III and intermediates between uroporphyrinogen III and coproporphyrinogen III (hepta-, hexa-, and penta-carboxyl porphyrinogens III)
Biochemical Finding:	A substantial increase in urinary and plasma porphyrins with a predominance of Uroporphyrin and Heptacarboxyl porphyrin.
Molecular/ Genetic Findings & Inheritance:	PCT results from an acquired deficiency of UROD in the liver. In most patients there is no genetic abnormality in UROD, and they are said to have type 1 or sporadic PCT. In PCT type 2 or familial PCT, there is a disease-causing mutation in the UROD gene inherited from one parent, leading to ~ 50% decrease in activity of the enzyme. This degree of decrease, however, does not lead to clinical disease; and additional factors that further decrease activity of hepatic UROD are required to cause PCT. — acquired or in familial cases autosomal dominant

SYMPTOMS

The symptoms of PCT are cutaneous, and there are no neurological symptoms. Blisters develop on sun-exposed areas of the skin, such as the hands and face. The skin in these areas becomes friable and may break down after minor trauma. These lesions heal poorly and tend to become secondarily infected. Increased hair growth, as well as darkening and thickening of the skin, may also occur. Liver function abnormalities are common but are usually mild. There may be progression to cirrhosis and even liver cancer. PCT is often associated with excess alcohol use and chronic hepatitis C, and genetic iron overload (hemochromatosis), which independently cause chronic liver disease.

DIAGNOSIS

The preferred screening test for PCT is measurement of porphyrins in plasma or urine. These are markedly increased and are predominantly uroporphyrin and heptacarboxyl porphyrin. Red blood cell porphyrins are normal or modestly increased. Fecal porphyrins may be modestly increased with an increased proportion of isocoproporphyrin. A mutation of UROD (inherited from one parent) is suggested by a family history of PCT and can be confirmed by DNA analysis. About 20% of PCT patients have a UROD mutation.

TREATMENT & PROGNOSIS

PCT is the most treatable of the porphyrias. Treatment is equally effective in types 1 and 2. Factors that tend to activate the disease (such as alcohol use) should be eliminated. PCT patients with active hepatitis C infection should be treated with one of the several highly effective direct-acting antiviral medications now available for treatment and cure of hepatitis C. Such drugs will nearly always also lead to prompt improvement in PCT. For patients without concurrent hepatitis C infection, the most widely recommended treatment is repeated phlebotomy (removal of blood), which will reduce the iron burden in the liver. Usually, the iron load is minor and treated by removal of just 3 to 6 pints of blood (one pint every ~2 weeks). Measurement of serum ferritin and plasma porphyrins are used to assess progress of this treatment. Phlebotomies are stopped when the ferritin falls to ~20 ng/mL. It is not necessary to continue phlebotomies after a remission has been achieved, but patients with hemochromatosis should have ongoing monitoring of ferritin for iron reaccumulation.

Another treatment approach is low-dose hydroxychloroquine, 100 mg (one- half of a 200 mg tablet), twice weekly. Usual higher dosage of this drug (as given for rheumatoid arthritis) is not needed and, in PCT patients, may cause transient but sometimes severe liver damage and worsening of photosensitivity. Hydroxychloroquine may be stopped ~2 months after plasma porphyrin levels become normal. PCT usually does not recur after treatment. Why some PCT patients relapse, and others don't sometimes relates to resumption of alcohol use and/or to increases of iron in the liver.

COMMON QUESTIONS & Answers

Q What Causes Porphyria?

A In each type of porphyria, there is an abnormality, usually a deficiency, of a specific enzyme. These enzymes are involved in the synthesis of heme, a substance important to many body functions and found in largest amounts in the bone marrow, red blood cells, and the liver. Heme is a key molecule upon which most life depends. It has many functions, mainly by binding to proteins, such as globin to form hemoproteins such as hemoglobin, in the bone marrow and red blood cells. Heme binds to numerous other proteins, which have an astonishing array of functions in the liver and other tissues and organs.

The type of porphyria present is determined by which enzyme is abnormal. These enzyme abnormalities are usually inherited deficiencies due to DNA mutations in the genes that encode for the proteins. But in one porphyria [X-linked protoporphyria or XLP] the abnormal enzyme is overactive, and in another [type 1 PCT] the DNA is normal, but the protein product of the gene is altered. Environmental factors, such as drugs, chemicals, diet, and sun exposure, can greatly influence disease severity, depending on the type of porphyria. Except for XLP, in which the mutation is found on the X [female sex] chromosome, the inherited porphyrias are either autosomal dominant (a single mutation, inherited from one parent, can cause disease) or autosomal recessive (two mutations, inherited from both parents, are necessary for disease to occur).

"Autosomal" genes always occur in pairs, with one coming from each parent. Individuals with an autosomal dominant form of porphyria have one abnormal gene paired with a normal one, and half of their offspring (on average) will inherit the gene for the disease, while the other half will inherit the normal gene. Some of those who inherit the abnormal gene will develop symptoms.

Q Is Porphyria Progressive or Fatal?

A Unlike some genetic diseases in which all individuals who inherit an abnormal gene become ill; the severity of porphyria varies considerably. Such variability is due to other genetic, environmental, or acquired factors in addition to the abnormal gene itself. Variations in other genes, presently mostly unknown, may also affect disease severity.

When symptoms are present, they can adversely affect quality of life. The complications of porphyria can be disabling, but with a prompt diagnosis and appropriate care, the disease is seldom fatal.

Q What Treatment and Prevention Are Available?

A Treatment depends on the type of porphyria. For most types, treatment is effective in the majority of individuals. Preventive measures, which, for the cutaneous types of porphyria include avoidance of sunlight, are of great importance. In the acute hepatic porphyrias, severe caloric restriction, as may occur during acute intercurrent illness or after bariatric surgery, certain drugs and excess alcohol may lead to acute attacks. Some women with acute hepatic porphyrias, unfortunately experience monthly acute attacks during the second half of their monthly menstrual cycles, due to the elevations of progesterone that occur at these times. Asymptomatic carriers of known disease-associated genetic mutations as well as patients who have symptoms should be educated about preventive measures.

Q Is Sunlight Always Harmful?

A Not for all types. People with acute intermittent porphyria are normally tolerant to sun. Those with a cutaneous porphyria, however, exhibit sun sensitivity, which appears either as blistering and scarring (for example, porphyria cutanea tarda) or an immediate painful reaction with little or no blistering (protoporphyria). Photosensitivity results from elevated levels of porphyrins in the skin and in circulating red blood cells, blood plasma or both. The excess porphyrins are produced by the liver or bone marrow (depending on the type of porphyria). Light interacts with and activates porphyrins in the skin to release energy that causes local damage and inflammation. Treatments to increase sun tolerance either lower porphyrin levels, interrupt the damaging effects of light-activated porphyrins, or increase skin pigment (eumelanin).

Q Should Doctors Be Informed That an Individual Has Porphyria, Even If It Is Latent?

A Yes! The diagnosis of porphyria is always an important item of medical information, even when there are no symptoms. It may, for example, influence the choice of drugs to treat other conditions, the choice of anesthesia for surgery, or dietary recommendations.

Q Is There Additional Risk if I Need Surgery or Become Pregnant?

A The risk of an attack of acute porphyria may be increased by surgery. This risk can be reduced if precautions are taken to avoid prolonged fasting [calorie restriction] and certain medications. Your surgeon and/or anesthesiologist may wish to consult with a porphyria expert prior to surgery. Such consultation may also be helpful during pregnancy. Although attacks of acute porphyria can occur during pregnancy, the risks can usually be managed successfully, and pregnancies can be brought to term with delivery of healthy infants. Acute attacks can be treated during pregnancy and are usually successful. Thus, as a rule, pregnancy is NOT contraindicated in women with acute hepatic porphyria.
People with EPP or XLP rarely develop liver failure. But are at risk of injury from exposure to high-intensity lights in the operating room. Surgical procedures in those with EPP/XLP should be performed under lights that are equipped with a yellow filter, to block the blue light that activates porphyrins.

See www.porphyria.org for more Frequently Asked Questions and Glossary of Terms.

Diagnostic TESTING

FIRST LINE TESTS

First line tests are used for screening, and if normal will exclude porphyria as the cause of current or recent symptoms. Second-line testing is recommended only if a screening test is abnormal.

• When abdominal and neurological symptoms suggest an acute porphyria, the best screening tests are urinary PBG, total porphyrins, and creatinine.

• When there are blistering cutaneous symptoms that suggest porphyria, the best screening test is a plasma or urine porphyrin and creatinine determination.

• For porphyrias that cause non-blistering photosensitivity (i.e., the protoporphyrias), the best screening test is measurement of erythrocyte (red blood cell) total protoporphyrin at a laboratory that does the correct test (see EPP-Diagnosis).

SECOND LINE TESTS

Second line complete biochemical testing includes urinary, fecal, and red blood cell porphyrins. It is advisable to have testing performed by a laboratory that has expertise in the clinical aspects of porphyria and that can provide an informed interpretation of the test results. Consultation with a porphyria expert is advised before a final diagnosis of acute porphyrias is accepted.

Measurement of heme biosynthetic enzymes in red blood cells is not appropriate for screening but may be used for family studies after someone with proven porphyria in the family is already known to have that enzyme deficiency. Such testing is being replaced by genetic testing.

GENETIC TESTING

Determination of the underlying mutation(s) by DNA sequencing is now standard of care for individuals in whom biochemical testing has indicated a diagnosis of porphyria. After a disease-causing mutation has been found in an index case, screening of other first-degree family members is strongly recommended to identify carriers of the same mutation[s] and at risk of acute porphyric attacks or other clinical manifestations. It is not recommended for screening individuals with symptoms suggestive of porphyria but no family history of the disease. The odds of finding a known porphyria-associated mutation in random individuals are extremely low. Another caveat is that DNA changes may be found that have never been associated with a case of porphyria but are reported as "genetic variants of uncertain significance" (pending further study). Patients may interpret such reports as "probably abnormal" and experience a great deal of anxiety. They and their providers are advised to contact a porphyria center, for guidance on biochemical testing for the type of porphyria under consideration and interpretation of these results together with the genetic test.

See www.porphyria.org for more information on Diagnostic Testing.

Scientific

ADVISORY BOARD

This information has been prepared and approved by members of the Scientific Advisory Board of the United Porphyria Association.

UNITED PORPHYRIAS ASSOCIATION
Advancing Awareness, Research & Therapies

4800 Hampden Lane, Suite 200
Bethesda, MD 20814

800-868-1292

info@porphyria.org

www.porphyria.org