Porphyria

Diagnosis and Treatment Options

What Is Porphyria?

The porphyrias are a group of seven rare diseases characterized by chronic skin manifestations (cutaneous porphyrias) or by intermittent acute attacks of illness (acute porphyrias).

Just how rare is Porphyria?

- Occurs in all races
- Acute porphyria occurs in about 1 to 2 people per 100,000
- High incidences reported in Sweden (AIP mostly) and South Africa (about 10,000 cases reported)

Types of Porphyria

Table 1-1: Types of porphyria (in order of frequency)

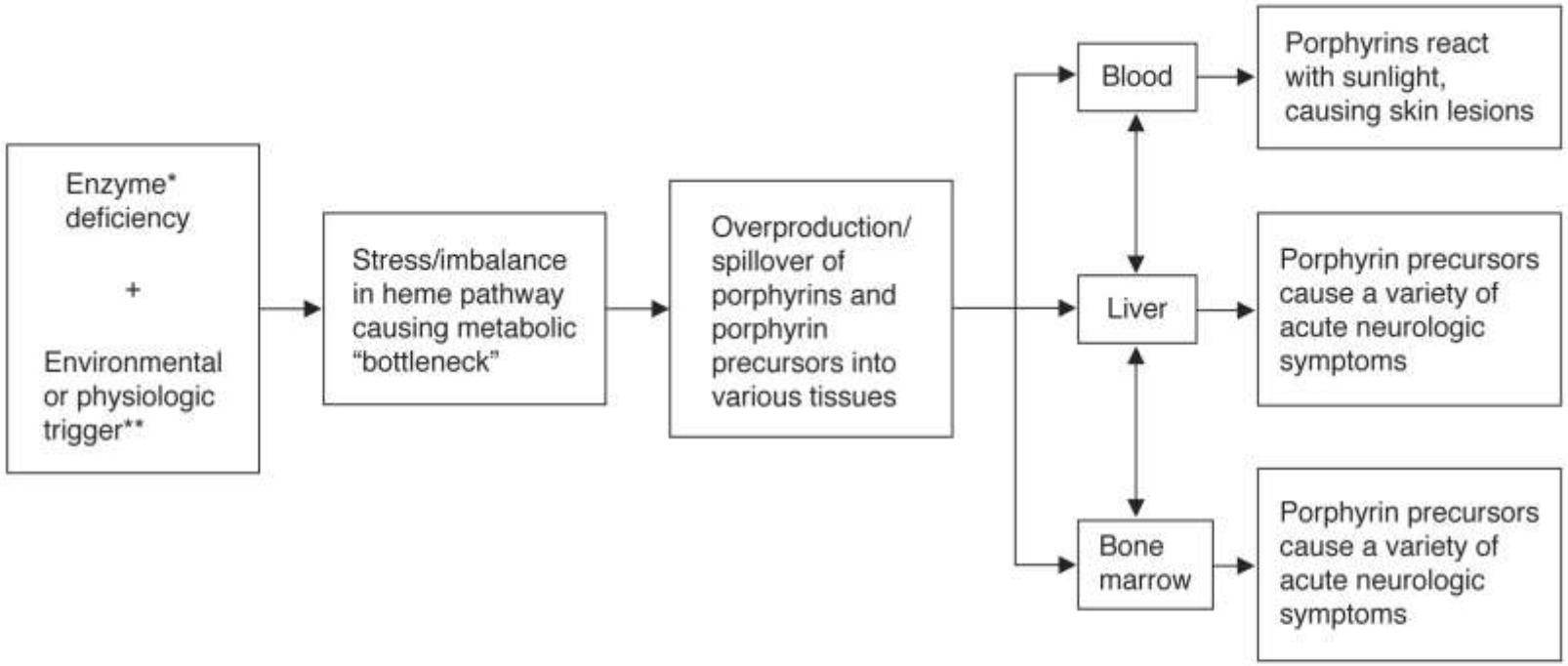
Porphyria type	Alternate names	Various classifications	Inheritance
Porphyria cutanea tarda	PCT	Cutaneous, hepatic, bullous, non-acute	Autosomal dominant*, incomplete penetrance; (extremely rare autosomal recessive form known as hepatoerythropoietic porphyria)
Acute intermittent porphyria (AIP)	AIP, Type II-A, Swedish porphyria, "the little imitator"	Acute, hepatic, neuropsychiatric	Autosomal dominant, incomplete penetrance
Erythropoietic protoporphyria	EPP, EP, congenital erythropoietic porphyria	Cutaneous, bullous, erythropoietic, non-acute	Autosomal dominant, incomplete penetrance
Variegate porphyria	VP, South African porphyria, porphyria variegata	Acute, hepatic, neurocutaneous, neuropsychiatric	Autosomal dominant, incomplete penetrance
Hereditary coproporphyria (HC)	HC, HPC, Copro	Acute, hepatic, neurocutaneous, neuropsychiatric	Autosomal dominant, incomplete penetrance
Congenital erythropoietic porphyria (CEP)	CEP, Gunther's disease	Cutaneous, bullous erythropoietic, non-acute	Autosomal recessive
Aminolevulinic acid dehydratase deficient porphyria	ALAD porphyria, plumboporphyria, Doss porphyria	Acute, hepatic, neuropsychiatric	Autosomal recessive

*80% of PCT patients do not have the familial variety

What Causes Porphyria?

- Deficiency of a particular enzyme involved in the synthesis of heme, the oxygen-carrying component of hemoglobin that is responsible for its characteristic coloring
- Deficiency + Other factors (drugs, diet, etc.)= overproduction of specific heme intermediaries known as porphyrins/porphyrin precursors
- Accumulation can cause mild to life-threatening symptoms

Pathophysiology of Porphyria

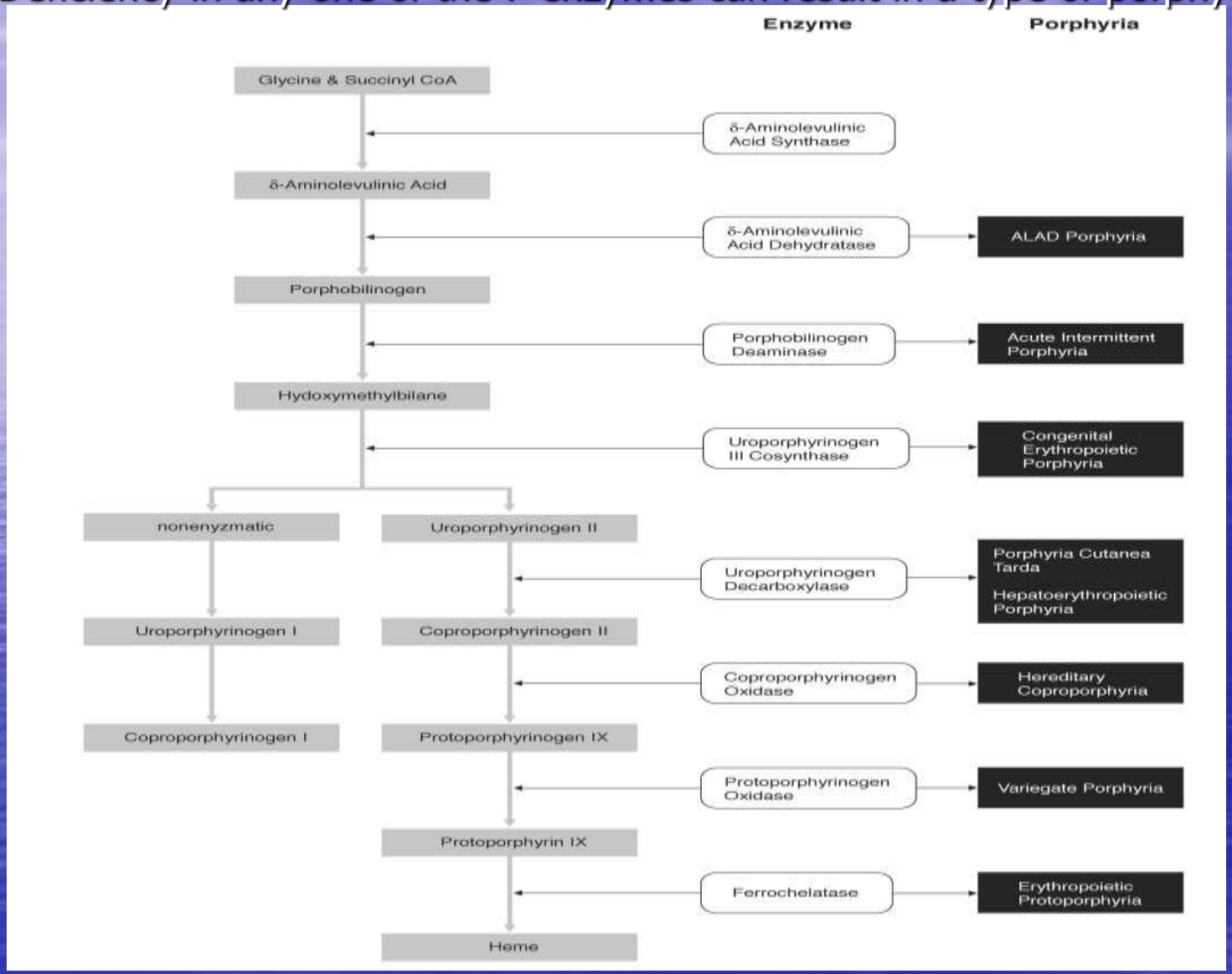


* Any of seven enzymes involved in the biosynthesis of heme

** Could be a particular medication, drop in nutritional intake, iron supplements, alcohol use, normal hormonal increase during menstrual cycle, etc.

Heme Biosynthetic Pathway

Deficiency in any one of the 7 enzymes can result in a type of porphyria



Reprinted from the American Porphyria Foundation (www.porphyriafoundation.com)

How do I get porphyria?

- In all but 1 of the porphyrias, Porphyria Cutanea Tarda (PCT), the enzyme deficiency is genetic.
- Patient inherits a defective gene from one or both parents

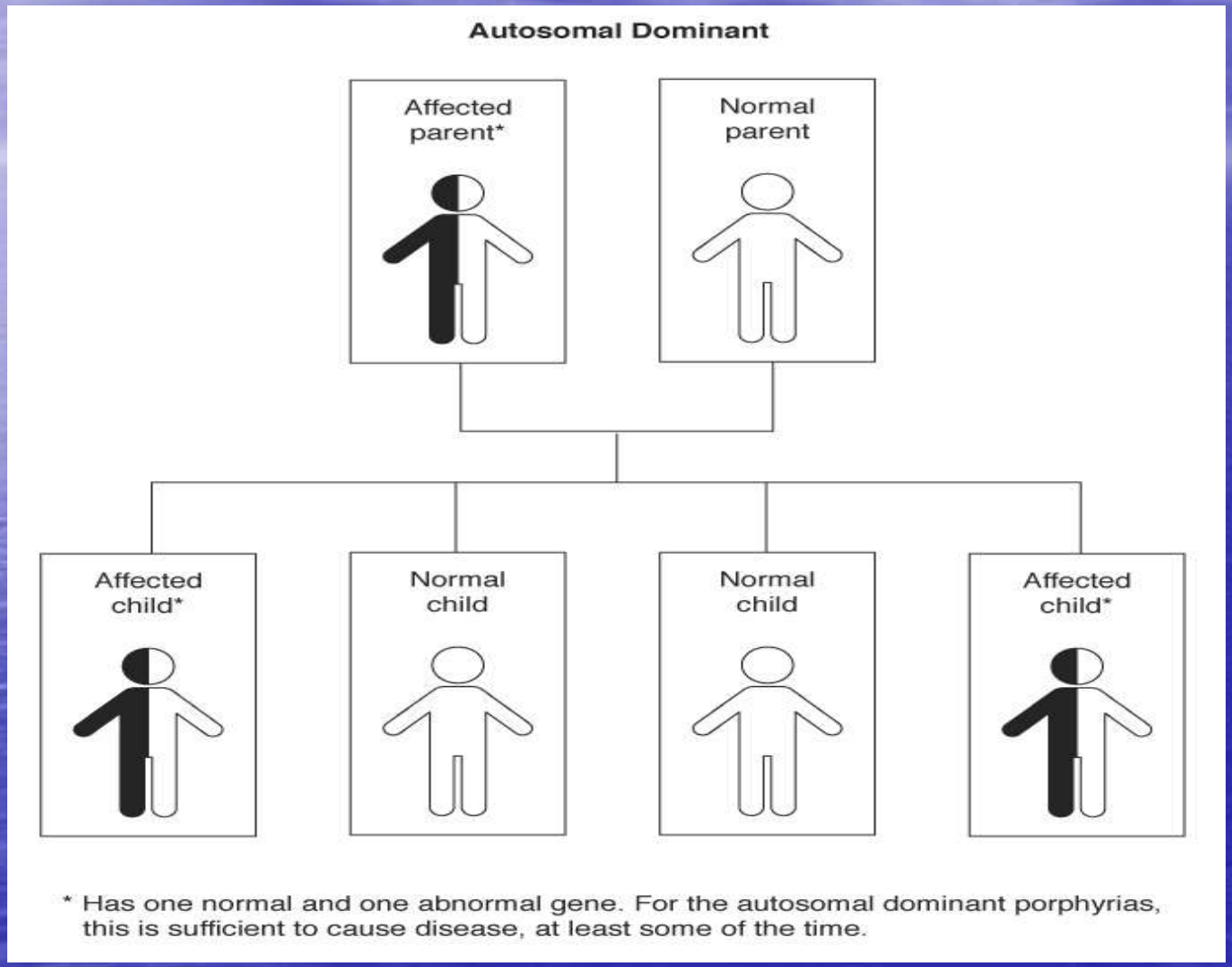
Autosomal Dominant

- Most are **Autosomal Dominant:** normal gene from one parent and abnormal from the other parent
  - Half the normal amt. of enzyme
  - Only 10-20% of people with 50% normal amount of enzyme ever develop clinical signs of porphyria

Autosomal Recessive

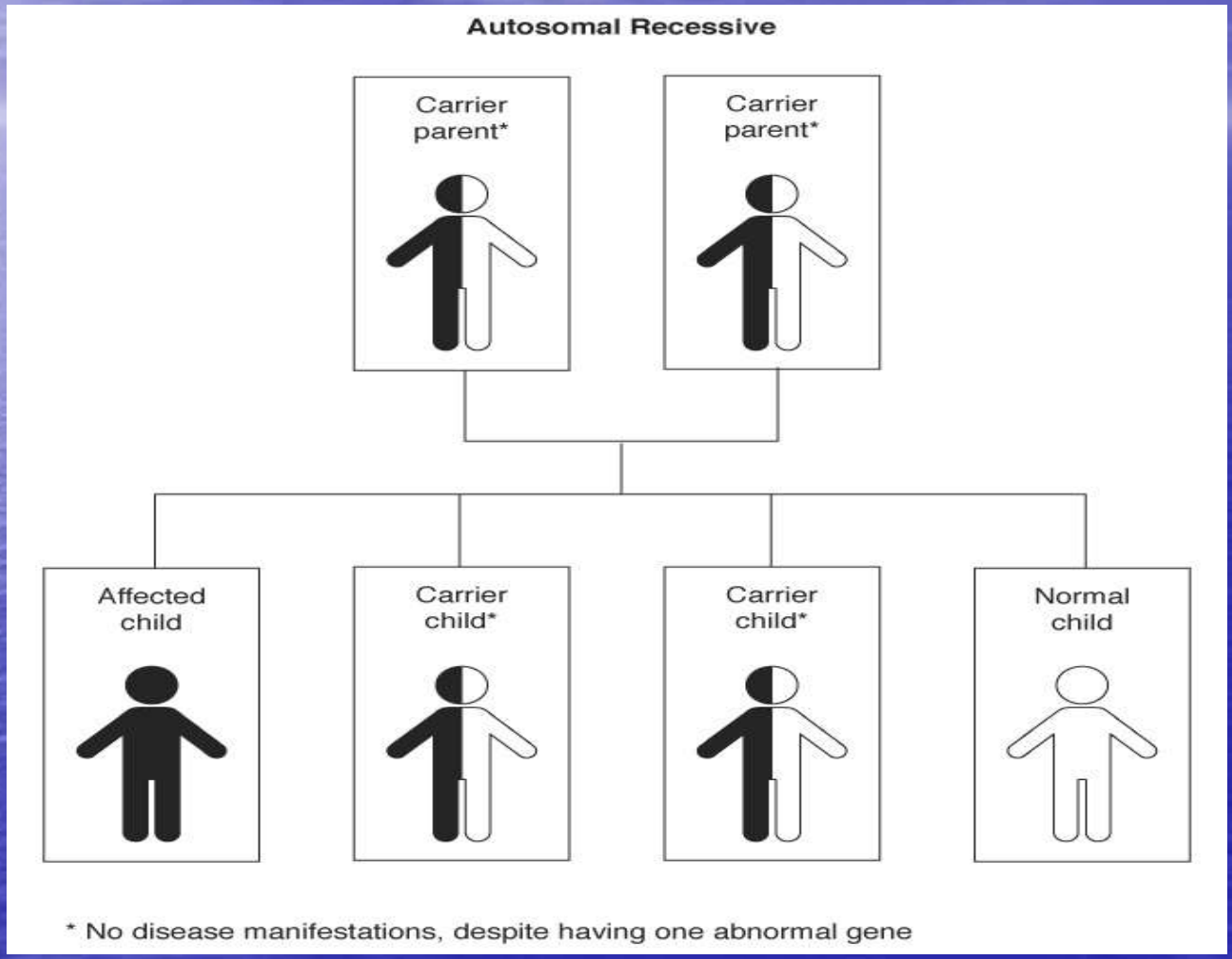
- Most rare & severe forms of porphyria
- Patient inherits a defective gene from both parents
- Virtual total lack of enzyme
- Offspring have a 25% chance of getting 2 defective genes, a 25% chance of getting 2 normal genes, and a 50% chance of getting 1 defective gene and 1 normal gene (usually means no illness)

Autosomal Dominant Inheritance



Images obtained from:
http://ghr.nlm.nih.gov/ghr/info/disorders/section/inheritance_patterns;jsessionid=7A08D6DF63D5412499CE7EBF695D1CD8

Autosomal Recessive Inheritence



Images obtained from:
http://ghr.nlm.nih.gov/ghr/info/disorders/section/inheritance_patterns;jsessionid=7A08D6DF63D5412499CE7EBF695D1CD8

Q & A

Question:

If your sibling has an autosomal recessive form of porphyria and you are healthy, what are the chances that you will have a child with your sibling's disease (assuming your partner does not also have a sibling with this same rare disease)?

Answer:

If you are not a carrier, the risk is 0. If you are a carrier (your chances are 2 out of 3), the only way you could have a child with the disease is if your partner was also a carrier. Thus, the risk is directly related to the carrier frequency in the general population

Types of Porphyria

- **7 major types: 3 cutaneous, 4 acute**
  - Porphyria Cutanea Tarda (PCT)
  - Erythropoietic Protoporphyria
  - Congenital Erythropoietic Porphyria
  - Acute Intermittent Porphyria (AIP)
  - Variegate Porphyria
  - Hereditary Coproporphyria
  - Aminolevulinic Acid Dehydratase-Deficient Porphyria

The Cutaneous Porphyrias

Patients develop mild to severe skin lesions upon exposure to sunlight due to reactions between excess porphyrins in the blood and UV light

Porphyria Cutanea Tarda

- Most common form of porphyria
- Deficiency of uroporphyrinogen decarboxylase
- Patients develop chronic blistering lesions on areas of the skin that are exposed to sun
- Generally begins in mid-adult life
- More common in men than women
- Precipitated by certain diseases or exposure to certain substances (alcohol, estrogen, iron..etc.)
- Usually treated by a course of phlebotomies (blood letting), which almost always produce a remission

Erythropoietic Protoporphyria

- 2nd most common cutaneous and 3rd overall
- Inherited deficiency of the enzyme ferrochelatase
- Patients experience burning, itching, swelling, and reddening of the skin within minutes of sun exposure
- Treatment is beta carotene

Congenital Erythropoietic Porphyria

- Very rare (fewer than 200 cases reported)
- Severe deficiency of the enzyme Uroporphyrinogen III cosynthase
- Manifestations are similar to PCT but are more severe and begin in early infancy

The Acute Porphyrias

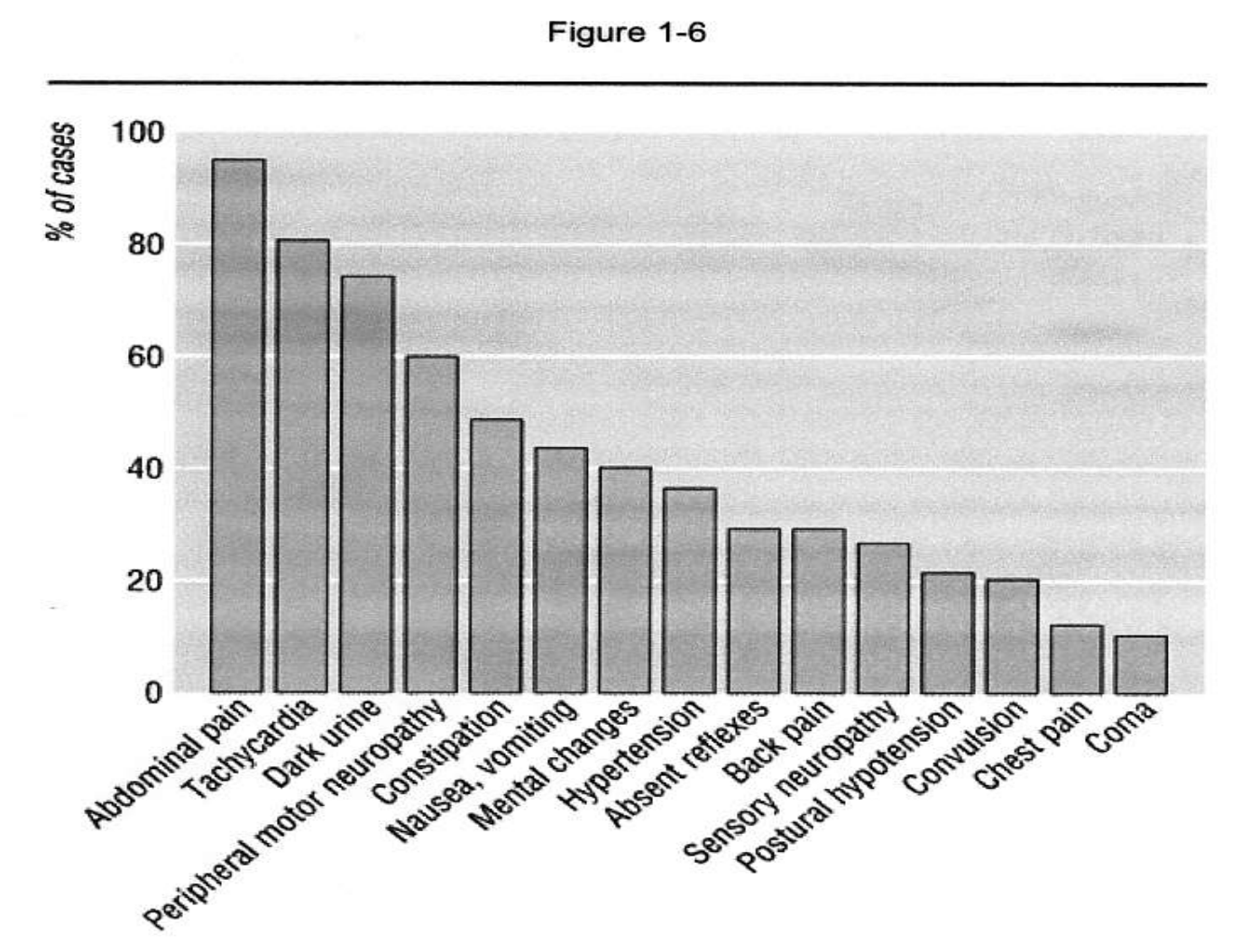
- 4 types, each caused by a different inherited enzyme deficiency
- Similar acute attacks
- All treated the same way
- Acute attacks can result in permanent neurologic damage or death if not treated properly and promptly

Potential precipitating factors

Table 1-2: Potential precipitating factors for acute porphyria

Factor	Comment
Numerous classes of drugs	Most notably barbiturates, sulfonamide antibiotics, many anti-convulsant drugs, and antihistamines. See Table 2-1 and www.porphyriafoundation.com for a more complete listing. Note that the status of newer drugs may not be established and that there is no universally accepted list of safe, unsafe, or potentially unsafe drugs in porphyria.[7]
Endogenous hormone levels	Some women are vulnerable to acute attacks during luteal phase of their menstrual cycle and/or during pregnancy because of normal changes in hormone levels.
Drop in caloric or carbohydrate intake	Patients with porphyria must keep to a balanced diet and should avoid crash dieting and fasting.
Illicit drugs	Marijuana, ecstasy, cocaine, and amphetamines can all trigger acute porphyria in some patients.
Smoking	Smoking causes exposure to certain chemicals that induce heme-containing enzymes and thus may stimulate heme synthesis.[3]
Alcohol use	Ethanol can induce ALA synthase, the first enzyme in the heme biosynthetic pathway.
Stress, infection	Can result in metabolic stress, impaired nutrition.

Symptoms of an Acute Attack



Reprinted with permission from Thandani, et al, BMJ 2000

Acute Intermittent Porphyria

- Most common of the Acute porphyrias, 2nd most common overall
- Results from a deficiency in the enzyme porphobilinogen deaminase
- AIP has a much higher incidence in some of the Scandinavian countries than in other parts of the world

Variegate Porphyria

- Results from a deficiency of protoporphyrinogen oxidase
- Photosensitivity and/or neuropsychiatric manifestations
- "South African porphyria" because incidence is so high in South Africa
- Patients with VP have less frequent and less severe acute attacks than patients with AIP

Hereditary Coproporphyria

- Deficiency of coproporphyrinogen oxidase activity
- Cutaneous and acute manifestations
- Less frequent and less severe acute attacks than in AIP
- Skin lesions occur in about a third of acute attacks and rarely occur independently

Aminolevulinic Acid Dehydratase-deficient Porphyria

- Extremely Rare (fewer than 10 cases reported in literature)
- Begins in childhood, unlike all other forms of acute porphyria

Difficulty of Diagnosing Acute Porphyria

- Often difficult since all symptoms of an acute attack can be due to other causes
- Many patients endure years of misdiagnosis
- Many patients are erroneously given a diagnosis of porphyria

Steps involved in diagnosing an acute attack of porphyria

Table 2-2: Steps involved in diagnosing an acute attack of porphyria

1. Exclude all other obvious causes of the patient's major symptoms (ie, appendicitis, ectopic pregnancy, lead poisoning, etc).
2. Determine index of suspicion on the basis of presenting symptoms, the patient's medical history, family history, the patient's age and gender, possible precipitating factors immediately prior to attack, etc. (keeping in mind that atypical presentations do occur).
3. If index of suspicion is high, obtain STAT urinary porphobilinogen (PBG) level (quantitative or semi-quantitative method recommended for accuracy).
4. If PBG level is elevated, withdraw all possible precipitating factors and begin heme therapy as soon as possible (mild attacks will sometimes resolve with glucose treatment).
5. While patient is being treated, order confirmatory tests, including a quantitative PBG on the same urine sample used earlier.

Adapted from Anderson 2000 and Thadani et al., 2000, p. 1648

4 reasons why Acute Porphyrias are missed or misdiagnosed

- ***Nonspecific symptoms***: symptoms of an acute attack can be caused by many other things
- ***Variable symptoms***: no single symptom or constellation of symptoms is universal in all patients
- ***Missing or incomplete Family History***: about 1/3 of the time, there is no family history of the disease because the disease has been latent for several generations
- ***Wrong tests are ordered and/or test results are not available promptly because they cannot be done on site***

Why is an accurate diagnosis of Porphyria so important?

- Prompt diagnosis is important because delays can result in irreversible neurologic damage
- Many of the medications used to treat the nonspecific symptoms of porphyria are drugs that can precipitate or worsen acute attacks
- Untreated attacks can result in long-term or permanent paralysis, coma, neurological damage, or even death

Harmful & Safe Drugs for Porphyria

Table 2-1: Categories of safe and unsafe drugs for porphyria*

Harmful drugs	Safe drugs
Barbiturates	Narcotic analgesics (morphine, meperidine, codeine, etc.)
Sulfonamide antibiotics	Aspirin and acetaminophen
Many tranquilizers and sedatives (eg, meprobamate, methyprylon, glutethimide)	Phenothiazines (eg, chlorpromazine)
Griseofulvin	Penicillin and derivatives
Some anti-epilepsy drugs (phenytoin, etc.)	Chloral hydrate
Birth control pills	Streptomycin
Alcohol	Glucocorticoids
Ergots	Bromides
Metoclopramide	Insulin
Rifampin	Atropine
Diclofenac	Cimetidine
Danazol	Serotonin reuptake inhibitor (antidepressants)

* Adapted with permission from the American Porphyria Foundation website (www.porphyriafoundation.com)

Biochemical tests for Porphyria

- *Watson Schwartz test*: screening test for elevated levels of PBG
- *Hoesch test*: screening test for elevated levels of PBG in urine
- *PBG trace kit*: shown to be considerably more sensitive and specific than the Watson Schwartz test; now recommended as the front-line screening test
- If PBG is elevated and the patient has symptoms of an acute attack, experts recommend that heme therapy should be started as soon as possible

Biochemical markers during an acute attack

Table 2-3: Biochemical markers during acute attack

Type of acute porphyria	Enzyme defect	Biochemical markers during acute attack			
		Urine	*Stool*	*Plasma*	*Erythrocytes*
Acute intermittent porphyria	PBG deaminase	↑PBG ↑ALA ↑Total porphyrins		↑PBG ↑ALA	*↓PBG synthase
Variegate porphyria	PROTO oxidase	↑PBG ↑ALA ↑COPRO ↑Total porphyrins	↑PROTO ↑COPRO ↑Total porphyrins	With skin lesions, ↑total porphyrins	
Hereditary coproporphyria	COPRO oxidase	↑PBG ↑ALA ↑COPRO ↑Total porphyrins	↑COPRO	With skin lesions, ↑total porphyrins	
ALA dehydratase-deficient porphyria	ALA dehydratase	↑ALA ↑COPRO ↑Total porphyrins	↑COPRO		*↓ALA dehydratase

*Also decreased in asymptomatic gene carriers and in symptomatic gene carriers between attacks
ALA denotes δ-aminolevulinic acid
COPRO denotes coproporphyrinogen oxidase
PBG denotes porphobilinogen
PROTO denotes protophyrinogen oxidase

DNA testing

- Mutation analysis is the "gold standard" of diagnosis for the acute porphyrias
- Major advantage is that it allows family members to determine if they have the defective gene, should they decide to be tested

Treating Acute Porphyria

- Acute attacks are treated the same way
- Treat symptoms as well as attempt to correct the heme biosynthetic pathway deficiency
- Intravenous glucose
- Heme therapy
- Withdraw precipitating or exacerbating factors

Glucose vs. Heme Therapy

- Historically, doctors have been advised to treat acute tacks first with intravenous glucose for a day or two and if symptoms don't resolve within 24 to 48 hours then institute heme therapy
- Today, however, clinical studies and expert opinion now lean toward beginning heme therapy right away
- Rationale is that heme therapy is more effective than glucose in reducing levels of porphyrin precursors during an acute attack
- In the United States, Panhematin is the only available heme therapy

Panhematin®
(hemin for injection)

- Developed by Abbott Laboratories
- Only FDA approved treatment for Acute Porphyria
- In 1983 became the first drug approved under the Orphan Drug Act for rare diseases
- Manufactured by Recordati Rare Diseases

(see next slide for ordering information)

Panhematin®
(hemin for injection)

To order Panhematin ®

Healthcare providers can place their order through their primary wholesaler or call 866.654.0539, fax 614.553.0539. Shipments will be delivered in a shipping box from ASD Healthcare via UPS Next Day Delivery. For patient assistance and support call 866.209.7604, M-F 8AM-5PM CT. RRD medical information (HCP's only)

contact 888.575.8344
or medinfo@recordatirarediseases.com.

Indication

Panhematin® (hemin for injection) is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women.

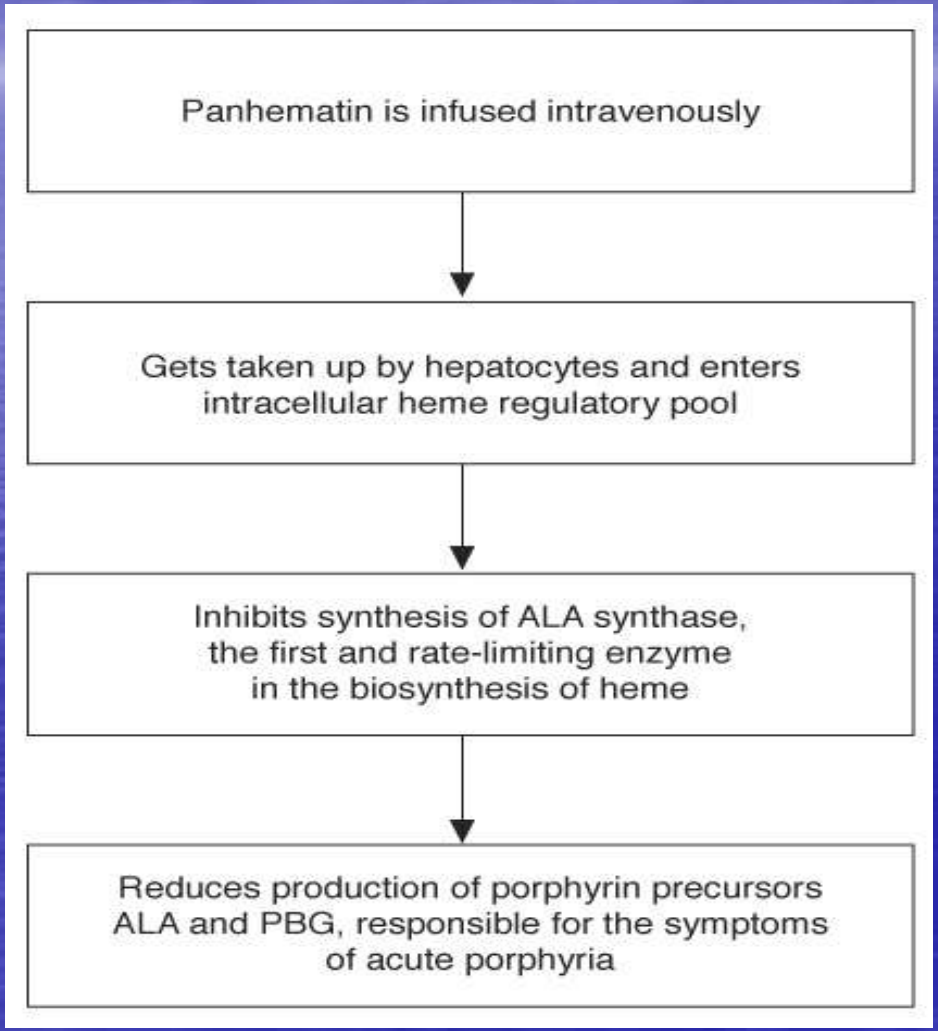
Manifestations such as pain, hypertension, tachycardia, abnormal mental status and mild to progressive neurologic signs may be controlled in select patients with this disorder.

Similar findings have been reported in other patients with acute intermittent porphyria, porphyria variegata and hereditary coproporphyria. Panhematin is not indicated in porphyria cutanea tarda.

How Panhematin Works

- Acute porphyrias are caused by an imbalance in the heme biosynthetic pathway
- Addresses the heme deficiency in the liver
- Reduces production of porphyrin precursors by repressing the enzyme ALA synthase

…How Panhematin Works



…How Panhematin Works

According to the Panhematin Package Insert…

”Heme acts to limit the hepatic and/or marrow synthesis of porphyrin. This action is likely due to the inhibition of δ-aminolevulinic acid synthetase, the enzyme which limits the rate of the porphyrin/heme biosynthetic pathway. The exact mechanism by which hematin produces symptomatic improvement in patients with acute episodes of the hepatic porphyrias has not been elucidated.”

Myths about Panhematin Treatment

Myth 1

Porphyria can be diagnosed by a Panhematin challenge…if a patient responds to Panhematin, this is evidence that he/she has acute porphyria.

Reality

- placebo effect
- spontaneous remission of symptoms during or immediately after treatment

Myths about Panhematin Treatment

Myth 2

During an acute attack, there is a "window of opportunity" for Panhematin treatment, after which it is ineffective.

Reality

Although some neuronal damage may be irreparable, Panhematin may help prevent further neurologic damage by addressing the biochemical imbalance causing the attack

Other Information/Educational Resources

- American Porphyria Foundation
  www.porphyriafoundation.com
- European Porphyria Foundation
  www.porphyria-europe.com
- Ovation Pharmaceuticals, Inc.
  www.ovationpharma.com
- NORD--National organization for Rare Disorders
  www.rarediseases.org