Porphyrias

Introduction

-The porphyrias are caused by deficiencies of enzymes involved in heme biosynthesis + other factors (drugs, diet , etc) which lead to blockade of the porphyrin pathway and subsequent accumulation of porphyrins and their precursors.

- Either genetic (autosomal dominant, autosomal recessive and X-linked) or acquired, occurs in all races
- Acute porphyria incidence is 1 to 2 people per 100,000
- Heterozygotes are asymptomatic in between acute attacks.
- Classified depending on site of overproduction and accumulation of porphyrin, overlapping features common

Hepatic

↓

- Neurologic, mental disturbances
- Abdominal pain
- Extremity pain, paresthesias
- Motor neuropathy

Erythropoietic

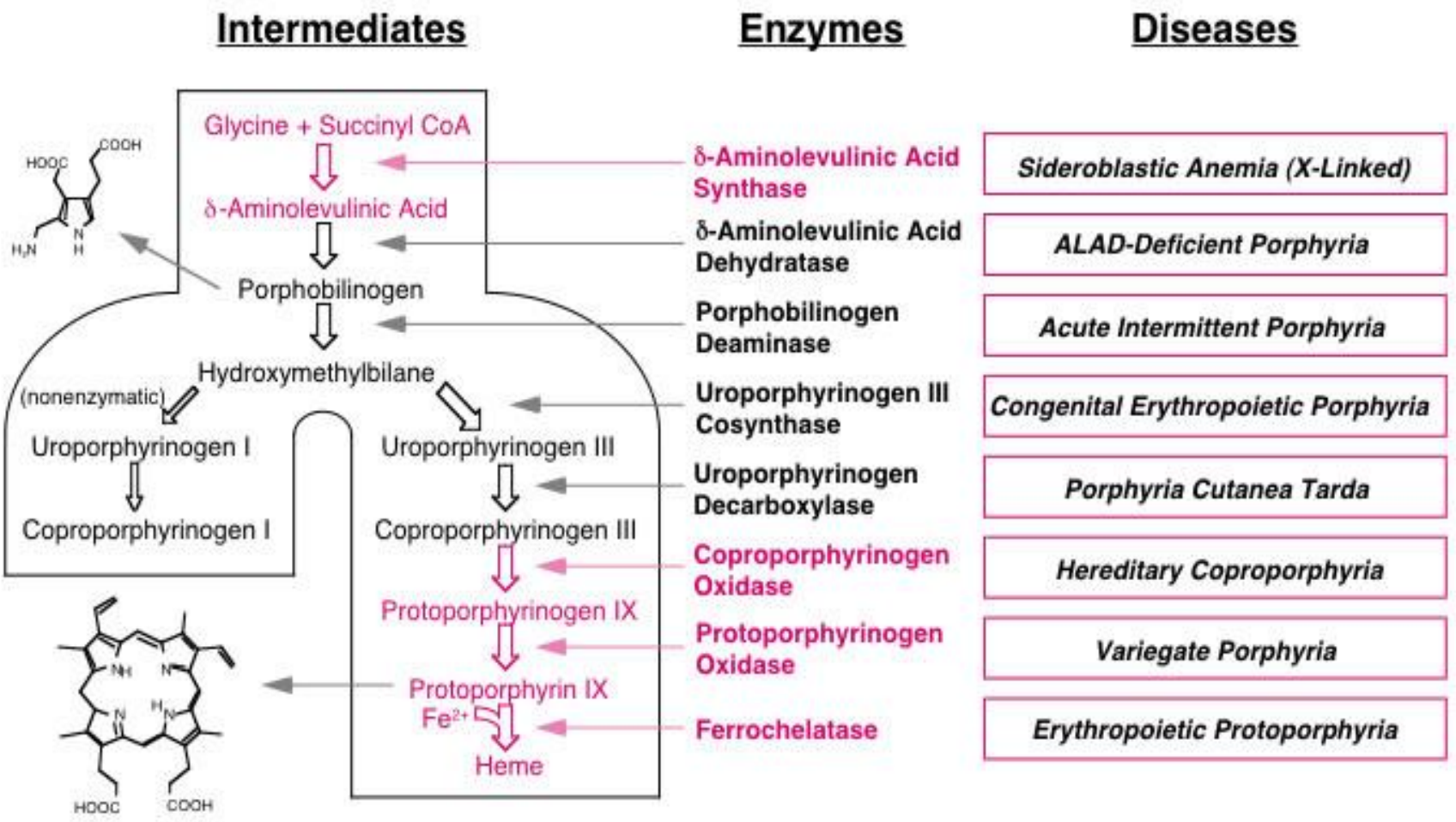
↓

- Cutaneous photosensitivity (long wave UV)
- light excites porphyrins in skins causing:

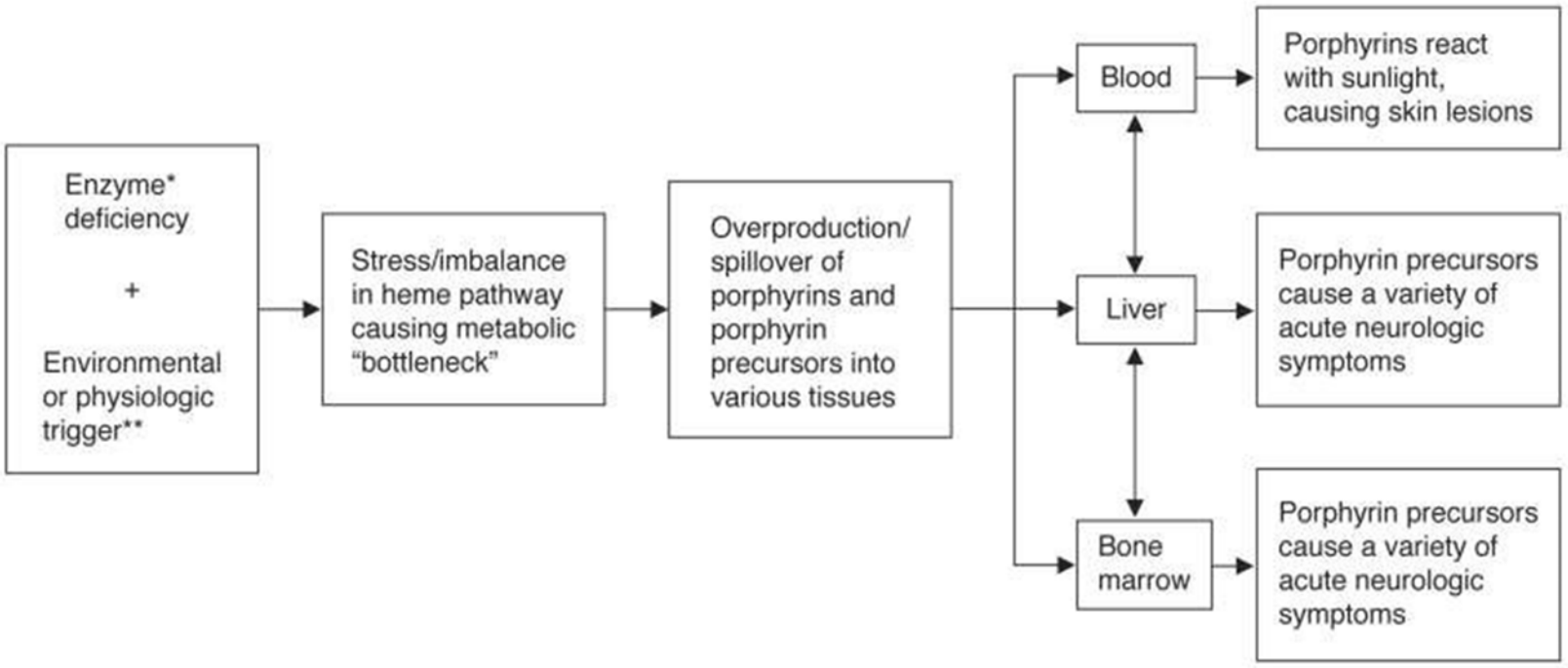
1- Cell damage

2- Hemolytic anemia

Heme Synthesis Pathway



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.

Classification of the Porphyrias

- Multiple ways to categorize porphyrias:
  - Hepatic vs. Erythropoietic: organ in which accumulation of porphyrins and their precursors appears
  - Cutaneous vs. Non- cutaneous
  - Acute and chronic forms
- Acute:
  - ALA dehydratase deficiency porphyria (ALAD)
  - Acute intermittent porphyria (AIP)
  - Hereditary coproporphyria (HCP)
  - Variegate porphyria (VP)
- Chronic:
  - Porphyria cutanea tarda (PCT)
  - Erythropoietic protoporphyria (EPP)
  - Congenital erythropoietic porphyria (CEP)
  - Hepatoerythropoietic porphyria (HEP)

Porphyria categories

A- Bone Marrow

- Erythropoietic protoporphyria
- Congenital erythropoietic porphyria

B- Liver

- Porphyria cutanea tarda
- Acute intermittent porphyria
- Variegate porphyria
- Hereditary coproporphyria
- Hepatoerythropoietic porphyria

Overview of the four acute porphyrias

- Four acute porphyrias cause acute, self-limiting attacks that lead to chronic and progressive deficits
- Symptoms of acute attacks increase the potential for misdiagnosis.
- Acute porphyrias are clinically indistinguishable during acute attacks, except the neurocutaneous porphyrias (variegate porphyria and hereditary coproporphyria) can cause dermatologic changes
- Acute attacks lead to an increase in PBG and ALA which can be detected in urine
- Diagnosis is difficult because of variable clinic course, lack of understanding about diagnostic process, and lack of a universal standard for test result interpretation

- Cutaneous features are not seen in acute intermittent porphyria or the very rare ALA dehydratase deficient porphyria.

- Erythropoietic protoporphyria and congenital erythropoietic porphyria are characterized by porphyrins produced mainly in the bone marrow.
- The reminder are primarily hepatic porhyrias.

- Excessive concentrations of porphyrins exposed to day-light generate free radicals, leading to cell membrane damage and cell death.

- The type of cellular damage depends on the solubility and tissue distribution of the porphyrins.

- Two main patterns of skin damage are seen in the porphyrias:
    1- accumulation of water soluble uro - and coproporphyrins leads to blistering.
    2- accumulation of the lipophilic protoporphyrins leads to burning sensations in the exposed skin.

Category	Type	Clinical presentation	Inheritance
Hepatic	ALA dehydratase deficiency	Acute attacks	Autosomal recessive
	Acute intermittent porphyria	Acute attacks	Autosomal dominant
	Porphyria cutanea tarda	Skin disease	Usually acquired; a minority are inherited (autosomal dominant)
	Hereditary coproporphyria	Skin disease, acute attacks	Autosomal dominant
	Variegate porphyria	Skin disease, acute attacks	Autosomal dominant
Erythropoietic	Congenital erythropoietic porphyria	Skin disease	Autosomal recessive
	Erythropoietic protoporphyria	Skin disease: specific presentation with immediate photosensitivity	Autosomal dominant: severe forms have complex inheritance

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.

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

Diagnosis

- Overlapping, may be difficult to determine exactly
- Check plasma, urine, stool porphyrin excretion, DNA testing

Porphyria	**Symptoms**	**Diagnostic findings** **U= Urine, F=Feces, E=Erythrocytes**
ALA dehydratase deficiency	Neurovisceral	↑ ALA (U)
Acute intermittent porphyria	Neurovisceral	↑ ALA and PBG (U)
Congenital erythropoietic porphyria	Photocutaneous	↑ uroporphyrin I and coproporphyrin I (U & E)
Porphyria cutanea tarda	Photocutaneous	↑ 7- carboxylate porphyrin (U) and isocoproporphyrin (F)
Hereditary coproporphyria	Photocutaneous and neurovisceral	↑ ALA, PBG and coproporphyrin (U) and coproporphyrin (F)
Variegate porphyria	Photocutaneous and neurovisceral	↑ ALA, PBG (U) and protoporphyrin (F)
Erythropoietic protoporphyria	Photocutaneous	↑ protoporphyrin (F & E) and in plasma

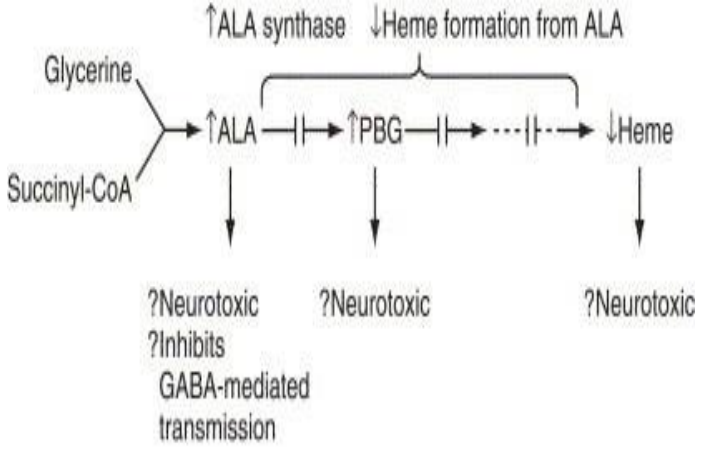
Acute intermittent porphyria

- Prevalence of 5-10 per 100,000 and thought to be higher in psychiatric populations
- More frequent in women than men.
- Heterozygotes are asymptomatic between acute attacks.
- Risk factors for exacerbation include medications, diet, weight loss, surgery, infection, menstrual hormones, smoking
- Common symptoms include:
    - Abdominal pain.
    - Tachycardia, arrhythmia.
    - Orthostatic hypotension.
    - Psychiatric symptoms including anxiety, depression, hallucinations and paranoia
    - Peripheral neuropathy

Diagnosis: Caused by a deficiency of PBG deaminase resulting in an accumulation of PBG and ALA

Treatment:

- Discontinue all unnecessary or potentially harmful drugs as Sulfa drugs, barbiturates, ACEI, Antiepileptics and Antifungals
- Treat any infection.
- Pain control with Morphine
- Treat sympathetic hyperactivity with propranolol.
- 300-400 grams of carbohydrates per day.
- IV heme at 3-5 mg/kg/day.

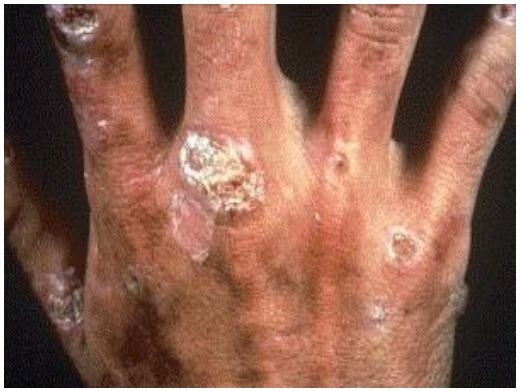


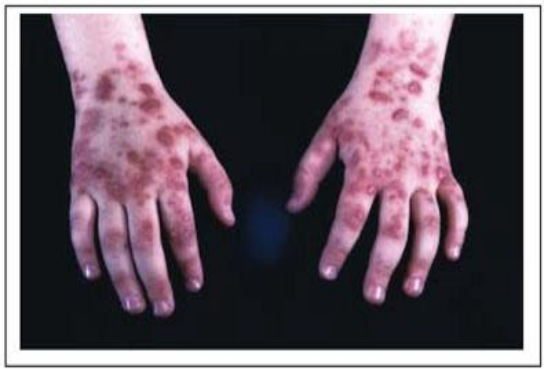
Porphyria cutanea tarda

- Most common porphyria which causes skin manifestations
- Deficiency of hepatic urodecarboxylase
- Cutaneous photosensitivity → fluid filled vesicles on sun exposed areas, friable skin, wounds heal slowly and hyperpigmentation on face
- No neurologic manifestations
- Higher incidence of hepatocellular carcinoma
- Precipitants frequently include alcohol, estrogen and iron

Treatment:

- Avoid sunlight, use sunscreen
- Chloroquine or hydroxychloroquine to form complexes with porphyrins to enhance excretion
- Superactivated charcoal
- β- carotene may increase tolerance of sunlight through Vitamin A.





Erythropoietic protoporphyria

- It is the most common childhood porphyria.
- It is usually evident by 2 years of age.
- Protoporphyrin levels are elevated because of deficient activity of ferrochelatase enzyme.

Congenital erythropoietic porphyria (Gunther's disease)

- It is a very rare autosomal recessive disorder.
- Patients usually present during infancy and rarely present in adult life with milder forms. Manifestations are similar to PCT but are more severe.
- It is caused by elevation of both water-soluble and lipid-soluble porphyrin levels due to deficiency of uroporphyrinogen III synthase enzyme.

Clinical features

-Very severe photosensitivity with phototoxic burning and blistering leading to burning sensation in the light exposed parts.

- Hypersplenism. - Hemolytic anemia. - Thrombocytopenia

Treatment

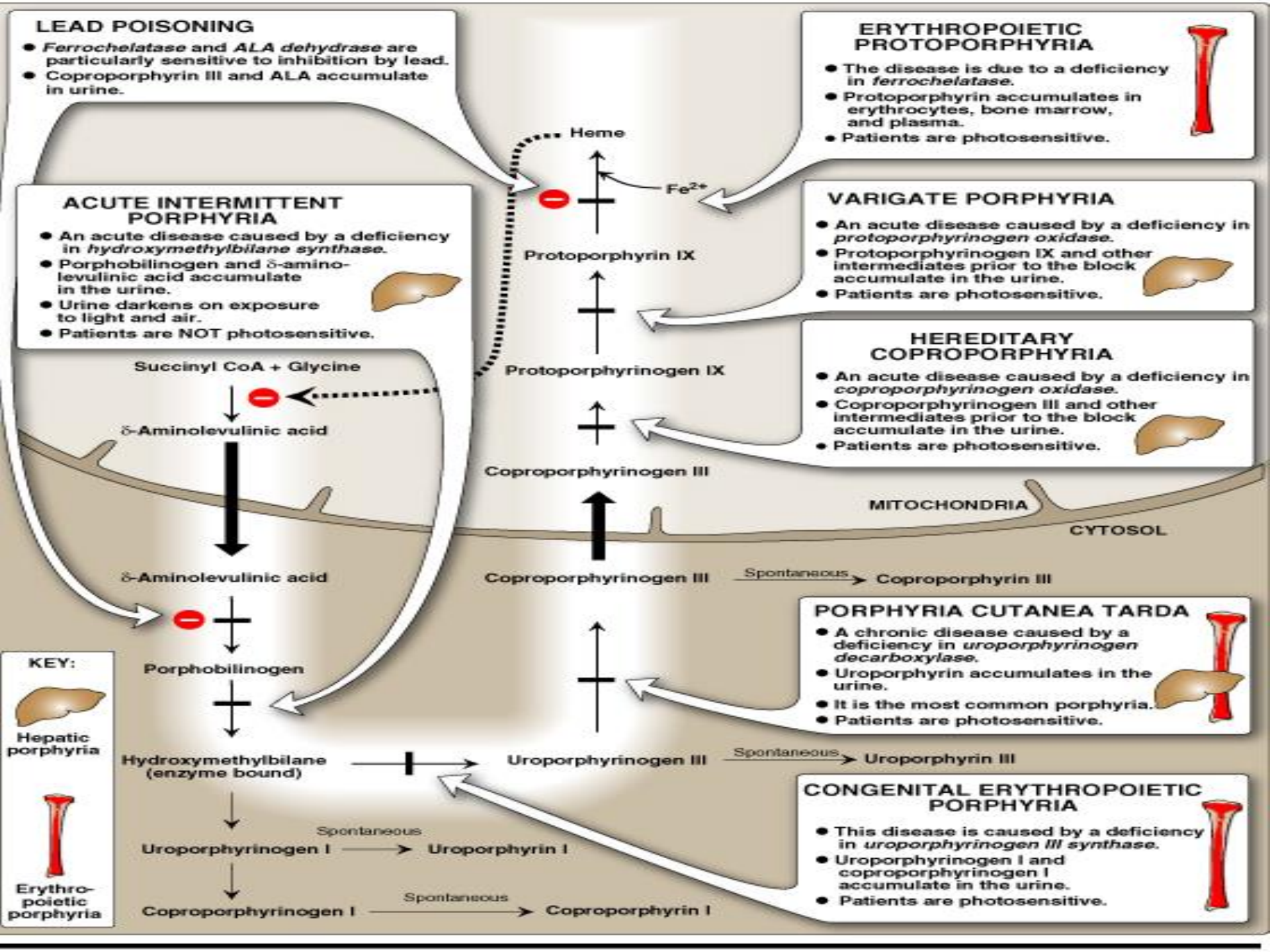
- Superactivated charcoal - Hypertransfusion
- Splenectomy - Bone marrow transplantation

Pseudoporphyria

- In certain settings patient develop blistering and skin fragility identical to PCT with the histological features but with normal urine and serum porphyrins.
-This condition called → pseudoporphyria.
- Most commonly due to medications especially NSAIDs and tetracycline.
- Some patients on hemodyalisis develop a similar PCT-like picture.

Neurotoxicity mechanisms

- Most current thinking focuses on accumulations of toxic metabolites.
- ALA and PBG are neurotoxins.
- ALA may be a false transmitter for GABA, it also blocks one of ATPases (perhaps a sodium pump).
- Another hypothesis: unsaturation of hepatic tryptophan pyrrolase secondary to liver heme deficiency leads to altered tryptophan delivery to CNS → ↑ tryptophan excretion.


LEAD POISONING
Ferrochelatase and ALA dehydrase are particularly sensitive to inhibition by lead.
Coproporphyrin III and ALA accumulate in urine.
ERYTHROPOIETIC PROTOPORPHYRIA
The disease is due to a deficiency in ferrochelatase.
Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
Patients are photosensitive.
Heme
Fe2+
ACUTE INTERMITTENT PORPHYRIA
An acute disease caused by a deficiency in hydroxymethylbilane synthase.
Porphobilinogen and δ-amino-levulinic acid accumulate in the urine.
Urine darkens on exposure to light and air.
Patients are NOT photosensitive.
Protoporphyrin IX
VARIGATE PORPHYRIA
An acute disease caused by a deficiency in protoporphyrinogen oxidase.
Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
Succinyl CoA + Glycine
Protoporphyrinogen IX
HEREDITARY COPROPORPHYRIA
An acute disease caused by a deficiency in coproporphyrinogen oxidase.
Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
δ-Aminolevulinic acid
Coproporphyrinogen III
MITOCHONDRIA
CYTOSOL
δ-Aminolevulinic acid
Coproporphyrinogen III
Spontaneous
Coproporphyrin III
PORPHYRIA CUTANEA TARDA
A chronic disease caused by a deficiency in uroporphyrinogen decarboxylase.
Uroporphyrin accumulates in the urine.
It is the most common porphyria.
Patients are photosensitive.
KEY:
Hepatic porphyria
Erythro-poietic porphyria
Porphobilinogen
Hydroxymethylbilane (enzyme bound)
Uroporphyrinogen III
Spontaneous
Uroporphyrin III
CONGENITAL ERYTHROPOIETIC PORPHYRIA
This disease is caused by a deficiency in uroporphyrinogen III synthase.
Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
Patients are photosensitive.
Spontaneous
Uroporphyrinogen I
Uroporphyrin I
Spontaneous
Coproporphyrinogen I
Coproporphyrin I