Porphyrias

- **Def:**

They r a group of inherited or acquired disorder in which the activity of enzymes in the haem synthesis pathway is

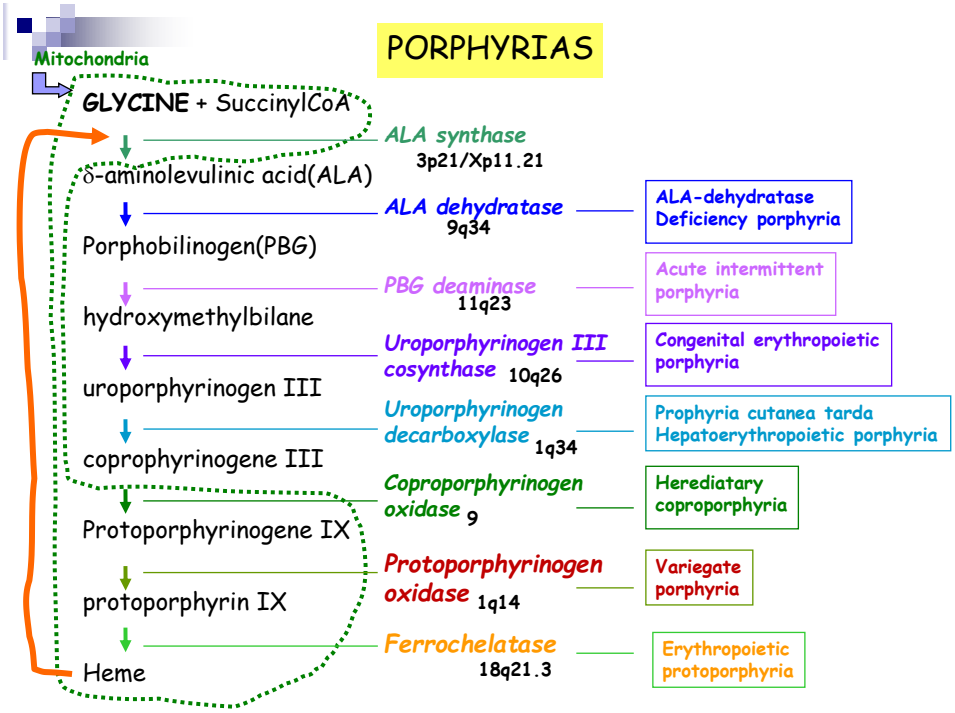
partially or completely deficient (↓).

- So it leads to:

- metabolic intermediates r ↑↑.

- accumulate in tissues.

- results in neurological &/or photocutenous symptoms.



Classification: → **liver**
→ **erythroid**

Erythropoietic Type (principal site of defect in erythroblast)	**Hepatic Type (principal site of defect in liver)**	
1-Congenital erythropoietic porphyria (CEP) **2-Erythropoietic protoporphyria (EPP).**	Acute 4	Chronic 2

Hepatic Type:

Acute (acute neurovisceral attacks)	**Chronic** (x acute attacks)
1-δ Amino-levulinic acid dehydratase porphyria (ADP). **2-Acute intermittent porphyria (AIP)** **3-Herediatry coproporphyria (HCP).** **4- Variegate porphyria (VP).**	**1-Porphyria cutanea tarda (PCT).** **2- Hepatoerythropoietic porphyria (HEP).**

PORPHYRIAS

- A group of rare disorders caused by deficiencies of enzymes of the heme biosynthetic pathway.
- There r 8 enzymes in heme synthesis, e' the exception of ALA (1st step), each enzyme defect leads to specific form of porphyria.
- The majority of the porphyrias are inherited in a autosomal dominant fashion - thus, affected individuals have 50% normal levels of the enzymes, and can still synthesize some heme.
- Affected individuals have an accumulation of heme precursors (porphyrins), which are toxic at high concentrations.

- Attacks of the disease are triggered by certain drugs, chemicals, and foods, and also by exposure to sun.

• Treatment involves administration of hemin, which provides negative feedback for the heme biosynthetic pathway, and therefore, prevents accumulation of heme precursors.

A- Erythropoietic Porphyria:

1- Congenital Erythropoietic Porphyria (CEP):

Aeitology:

Rare, AR

Partial or complete def. of uroporphyrinogen III cosynthase activity.

C/P:

Starts in infancy

-cutanous photosensitivity,dermatitis,alopecia

-red teeth (red flourescent under UV light pathognomonic)

-H.A, splenomegaly, porphyrin rich gall stones

-pathologic fractures & short stature.

Diagnosis:

In utero: dark brown porphyrin rich amniotic fluid.

In newborn: pink-dark brown staining of diapers.

Urine: ↑ urinary potphyrin excretion (uroporphyrin) 20-60 folds N.

Feces: ↑fecal porphyrin.

ttt:

-avoid sunlight, skin trauma, use topical sunscreens, β carotene (↓ photosensitivity).

-BM suppression e' high level transfusion.

-Spleenectomy

-Fe chelation to ↓ porphyrin synthesis.

2-Erythropoietic Protoporphyria (EPP):

Pathogenesis: -AD

↓ Ferrochelatase activity due to missense or deletion of the gene.

C/P:

-starts in childhood

-cutanous photosensitivity esp. on face & hands but milder than others.

-Burning edema, itching of skin after light exposure (ppt F.)

-xH.A but mild microcytic an.

-Gall stones common.

-Liver cirrhosis, liver failure.

-x neurological symptoms.

Lab findings:

- ↑ protoporphyrin in RBCs, plasma, BM, bile & feces.

- urinary porphyrin N.

ttt:

as before.

B- Hepatic Porphyrias:

I- Acute:

1- ALA Dehydratase deficiency Porphyria (ADP):

Pathogenesis: Rarest type

AR, ↓or x ALA dehydratase (diff. point mutation).

C/P:

Rarest form (only 4 cases r reported).

-neurovisceral symptoms (see AIP).

-clinical exacerbations following stress, ↓ caloric intake.

Lab findings:

- ↑ Urinary ALA execration.

-Red cell ALA dehydratase activity less than 2% N (**Diagnostic**).

ttt:

as AIP.

2-Acute Intermittent Porphyria (AIP):

Pathogenesis:

AD

Partial def. of **Porphobilinogen deaminase**

C/P: Most disabling form of Porphyria

-Abdominal pain.

-Nausea, vomiting, constipation or diarrhea.

-Neuropathy: may be motor or sensory → bulbar paralysis, respiratory distress, muscle weakness, seizures, and mental symptoms.

-↑B.P, ↑HR, ↑ temp.

-Attacks may last from few days to several months.

-Attacks may ppt. by:

- ↓Caloric intake esp. carbohydrates.
- Estrogen, progesteron, puberty, menses.
- Infection, alcohol, surgery, drugs e.g: Phenobarbital.

-Urine may be Port-wine red (porphobilin).

Lab findings:

- ↑ ALA, ↑PBG in urine.
- ↓PBG deaminase in all tissues.

ttt:

-Adequate nutrition & caloric intake.

-Avoid ppt. factors & drugs, ttt infection.

-Unresponsive cases:

-admit to hospital.

-glucose I.V.

-Hematin I.V.

-Luteinizing hormone → x ovulation, ↓ premenstrual attacks.

3-Herediatry Coproporphyria (HCP):

Pathogenesis:

- AD
- ↓ **Coproporphyrin oxidase**.

C/P:

-Photosensitivity in 30% of patients.

- Neurologic manifestations as AIP.

-Attacks ppt by:

-menses, pregnancy, contraceptive steroids.

- drugs e.g: phenobarbital.

Lab findings:

-↑Urinary, fecal excretion of coproporphyrin III.

-↑ Urinary excretion of ALA, PBG, uroporphyrin during attacks.

ttt:

-avoid ppt factors.

- ttt acute attacks as AIP.

4-Variegate Porphyria (VP):

Pathogenesis:

-AD

- ↓ Protoporphyrinogen oxidase.

C/P:

- Photosensitivity.

- Neurovisceral symptoms as AIP.

- ppt by same factors as AIP.

Lab findings:

- ↑Fecal execration of porphrin esp. protoporphyrin IX.

- ↑ Urinary execration of coproporphyrin , ALA, PBG during attacks.

- Plasma contains a porphyrin e' **Fluorescence max at 626 nm {Specific for VP}.**

ttt:

As before for photosensitivity & neurovisceral attacks (see AIP).

II- Chronic Hepatic Porphyria:

1- Porphyria Cutanea Tarda (PCT):

Pathogenesis:

- **Most common** porphyria.

- **Uroporphyrinogen (URO) decarboxylase.**

Types:

Type I: sporadic, adults, enzyme in liver but N in RBCs.

Type II: AD, children or adults, enzyme in both RBCs & liver.

Type III: children or adults, enzyme in liver but N in RBCs.

C/P:

-Photosensitivity, dermatitis, alopecia.

- Liver cirrhosis ⟶ hepatoma.

- Liver biopsy shows hemosiderosis, ↑serum Fe, ↑ serum ferritin.

- Sporadic PCT ppt. by alcohol, estrogen, pregnancy.

Lab findings:

- ↑Urinary porphyrin.

- ↑Fecal isocoproporphyrin.

ttt:

-as before, avoid ppt. factors.

- Phlebotomy to Fe stores.

2- Hepatoerythropoietic Porphyria (HEP):

Pathogenesis:

- Rare AR
- ↓**Uroporphyrinogen decarboxylase**.

C/P: as CEP

- childhood onset e' pink urine.
- severe phoyosensitivity, skin fragility.
- HSM.
- H.A.

Lab findings:

- ↑ Urinary porphyrin.
- ↑ isocoprophyrin in feces.
- ↓URO decarboxylase activity to 2-10% N level.

ttt:

As before.

Table: Porphyrias:

Type	Enzyme Involved	Major Symptoms	Laboratory tests
Acute intermittent porphyria	Uroporphyrinogen synthase	Abdominal pain Neuropsychiatric	**urinary porphobilinogen** ⇑
Congenital erythropoietic porphyria	Uroporphyrinogen cosynthase	Photosensitivity	**urinary uroporphyrin** ⇑ **porphobilinogen** ⇔
Porphyria cutanea tarda	Decarboxylase	Photosensitivity	urinary uroporphyrin ⇑ porphobilinogen ⇔
Variegate porphyria	Oxidase	Photosensitivity Abdominal pain Neuropsychiatric	urinary uroporphyrin ⇑ fecal coproporphyrin ⇑ fecal protoporphyrin ⇑
Erythropoietic protoporphyria	Ferrochelatase	Photosensitivity	