Porphyria: clinical presentations,diagnosis and treatment

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Porphyria

- **Introduction**

- Classification
  - Acute porphyria
  - Cutaneous porphyria
  - Rare recessive porphyrias

- Conclusion

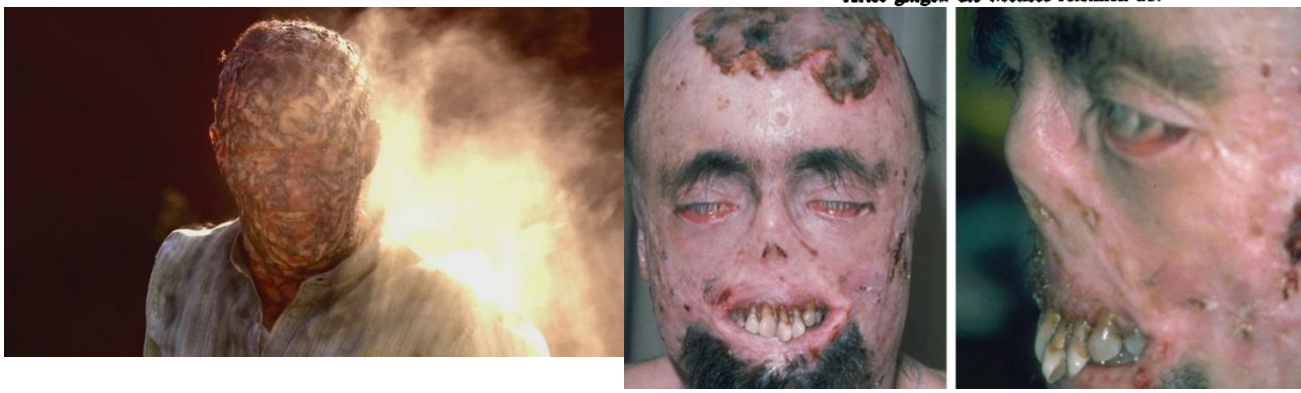
History

- *Porphyra:* purple pigment
- Described by Hippocrates
- 1871, Felix Hoppe-Seyer: causal link with porphyrine
- 1889, Dr. Stokvis: porphyria as a clinical syndrome
- King George III
- Vampires and werewolves

Table 1. Translations (see text) from "Hippocrates. Epidemics Book III" (Oeuvres complete d'Hippocraté. Ed. Emile Littré. Vol. 3, Paris 1841, Repr. Amsterdam 1978, case XI, 134–135)

Case XI

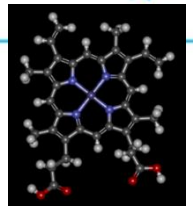
In Thasos a woman of gloomy temperament, after a grief with a reason for it, without taking to bed lost sleep and appetite, and	Auf Thasos hatte eine Frau von schwermütiger Veranlagung aus besonderem anlass einen Kummer. Da befiel sie Schlaf- und Appetitlosigkeit, starker
suffered thirst and nausea. She lived near the place of Pylades on the plain.	Durst und Übelkeit, ohne dass sie sich niederlegen musste. Sie wohnte auf dem Flachland nahe bei Pylades.
First day. As night began there were fears, much rambling,	Am ersten Tag zu Beginn der Nacht bekam sie Angstzustände, redete viel,
depression and slight feverishness. Early in morning frequent convulsions; whenever these frequent convulsions intermitted, she wandered and uttered obscenities;	litt unter Depressionen, die Temperatur war etwas erhöht. Morgens hatte sie mehrfach Krämpfe. Sooft die Krämpfe etwas nachliessen, redete sie irr und führte unanständige Reden. Sie hatte
many pains, severe and continuous. Second day. Same symptoms; no sleep; fever more acute.	viel starke, anhaltende Schmerzen. Am zweiten Tag ebenso, sie konnte nicht schlafen, das Fieber stieg.
Third day. The convulsions ceased, but were succeeded by coma and	Am dritten setzten die Krämpfe aus, doch litt sie an Schläfrigkeit und
oppression, followed in turn by wakefulness. She would jump up; could not restrain herself; wandered a great deal; fever acute, on this night a copious, hot sweating all	Ershöpfung; dann wieder war sie hellwach, sprang auf, konnte sich nicht halten, führte viel irre Reden, hatte hohes Fieber; in dieser Nacht hatte sie einen starken Ausbruch on warmem
over; no fever, slept, was perfectly rational, and had a crisis. About the third day urine black and thin, with particles mostly round floating in it, which did not settle. Near the crisis copious menstruation.	Schweiss am ganzen Körper. Sie war fieberfrei, schlief, war vollkommen klar, die Krise trat ein. Am dritten liess sie dünnen, dunklen Urin, darin schwamm en weitausgebreitet runde Teilchen, die sich nich setzen. Während der Krise gingen die Menses reichlich ab.



Porphyria

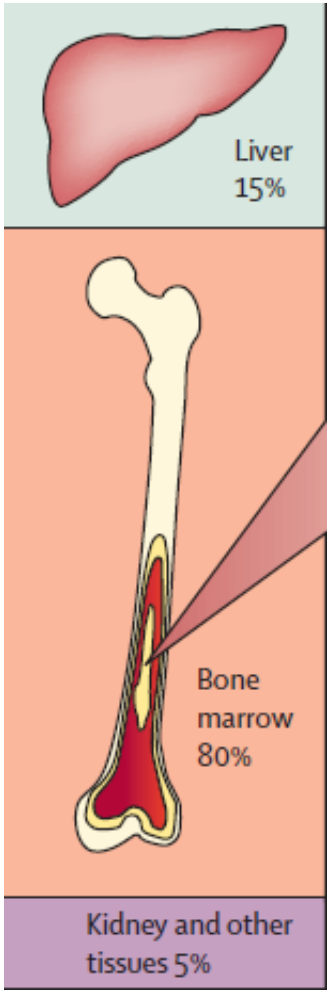
- Metabolic disease
- Defect in 1 of the 8 enzymen involved in synthesis of haem
- Build up of haem precursors

  -> symptoms (neurovisceral and/or cutaneuous)
- Inborn - acquired

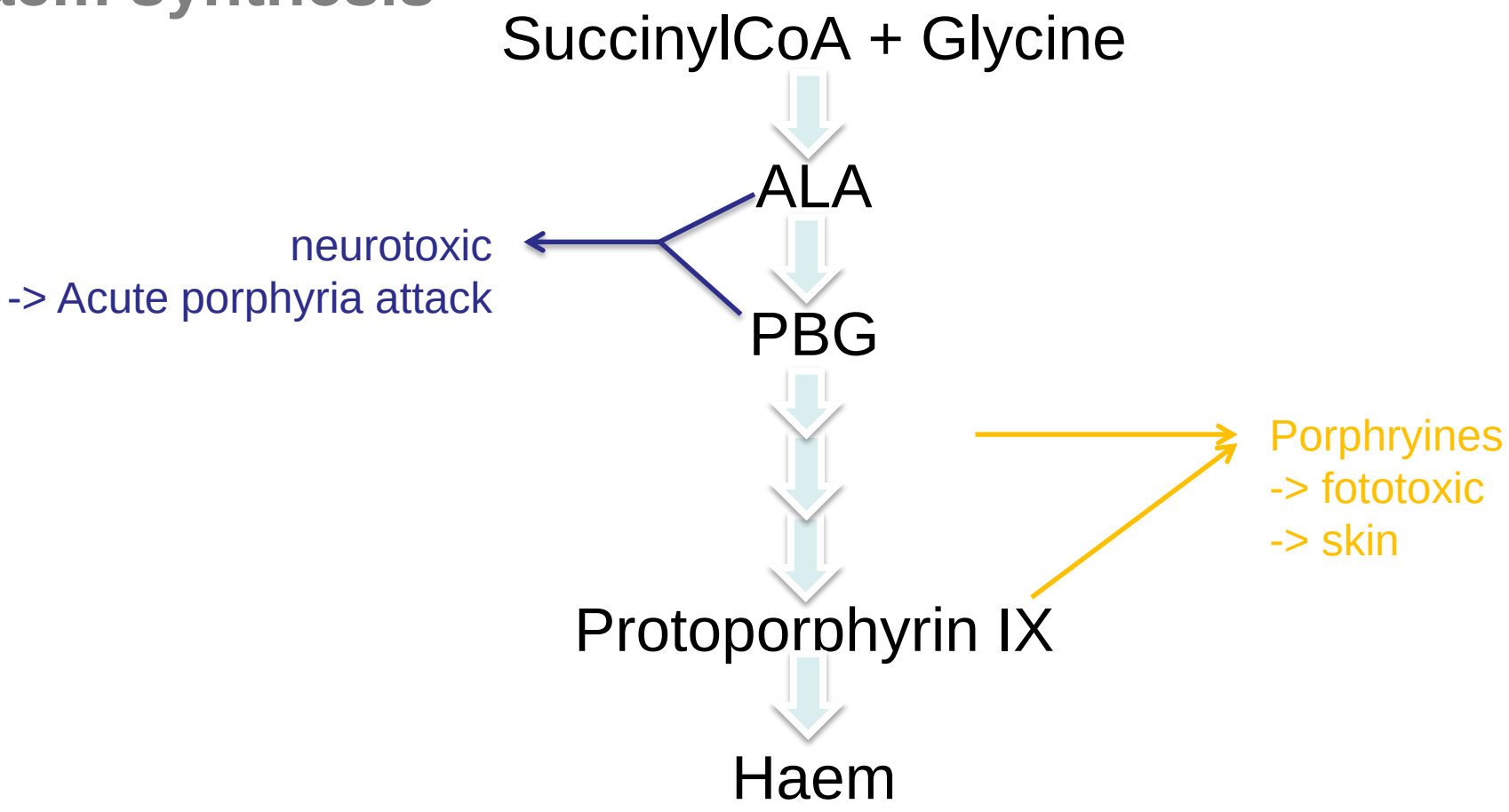


Haem

- Synthetized in every cell
- 80% in bone marrow (hemoglobin)
- 15% in liver: production of cytochrome P450 enzymes (CYP's)
- Other haem-containing proteins:
  myoglobin, respiratory cytochrome, catalase, NO-synthase



Haem synthesis



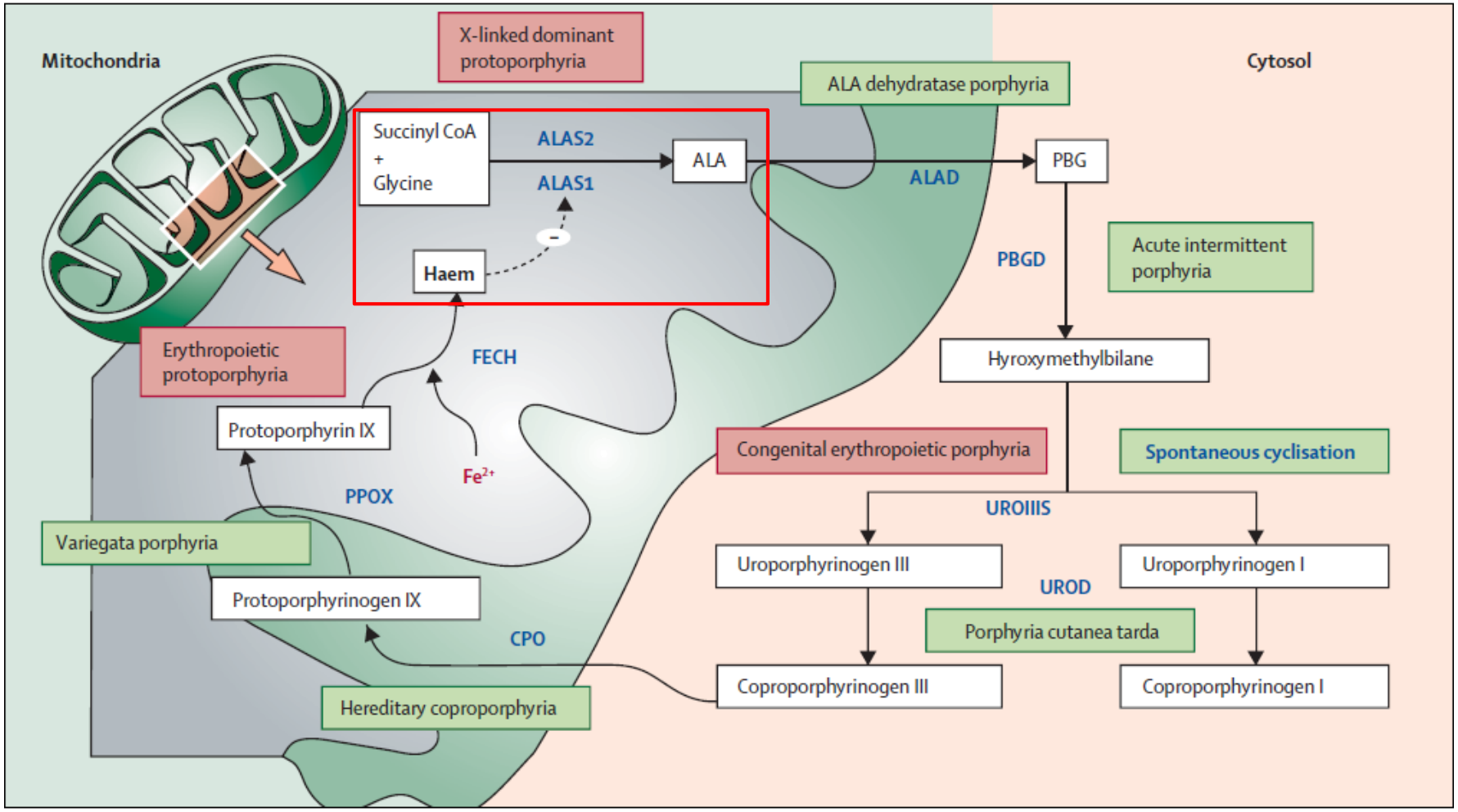
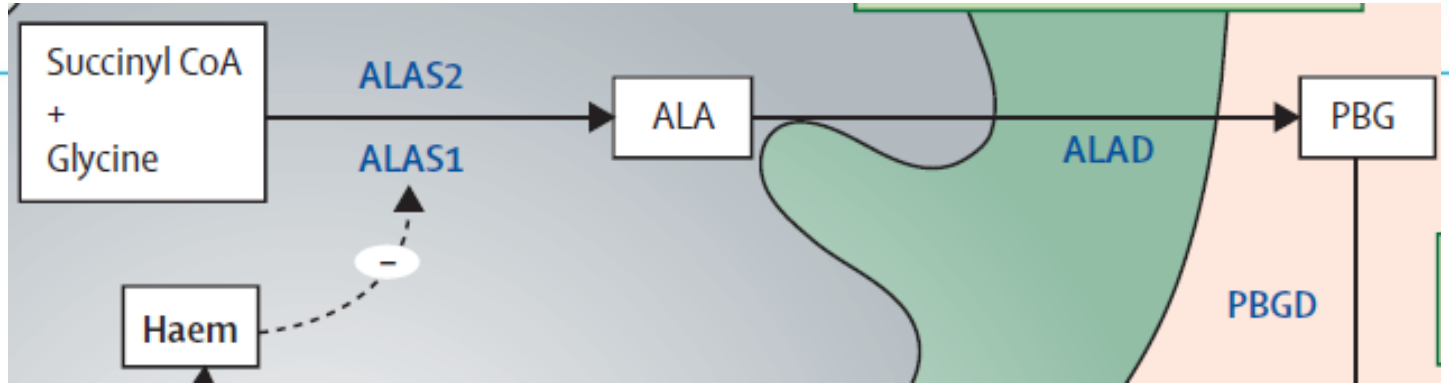


Figure 1: **Haem biosynthetic pathway and porphyrias**
Green boxes=hepatic porphyrias. Red boxes=errythropoietic porphyrias. ALA=5-aminolaevulinic acid. PBG=porphobilinogen. I, III, or IX=type isomers. ALAS=ALA-synthase. ALAD=ALA-dehydratase. PBGD=porphobilinogen deaminase. UROIIIS=uroporphyrinogen III synthase. UROD=uroporphyrinogen decarboxylase. CPO=coproporphyrinogen oxidase. PPOX=protoporphyrinogen oxidase. FECH=ferrochelatase. Fe^{2+}=ferrous iron.

- Regulation



  - **ALAS1**: *in liver and other cells*
    - Rate limiting enzyme
    - Negative feedback by haem (R/haemtreatment in acute porphyria)
    - Haem required for CYP's

      -> induction of CYP's (bv medication,...) -> induction of ALAS1
  - **ALAS2**: *only in ertythroblasts in bone marrow*
    - No inhibition by haem
    - Dependent on iron and EPO availibility
  - (**ALAD:** inhibited by lead, tyrosinaemia type I)

Porphyria

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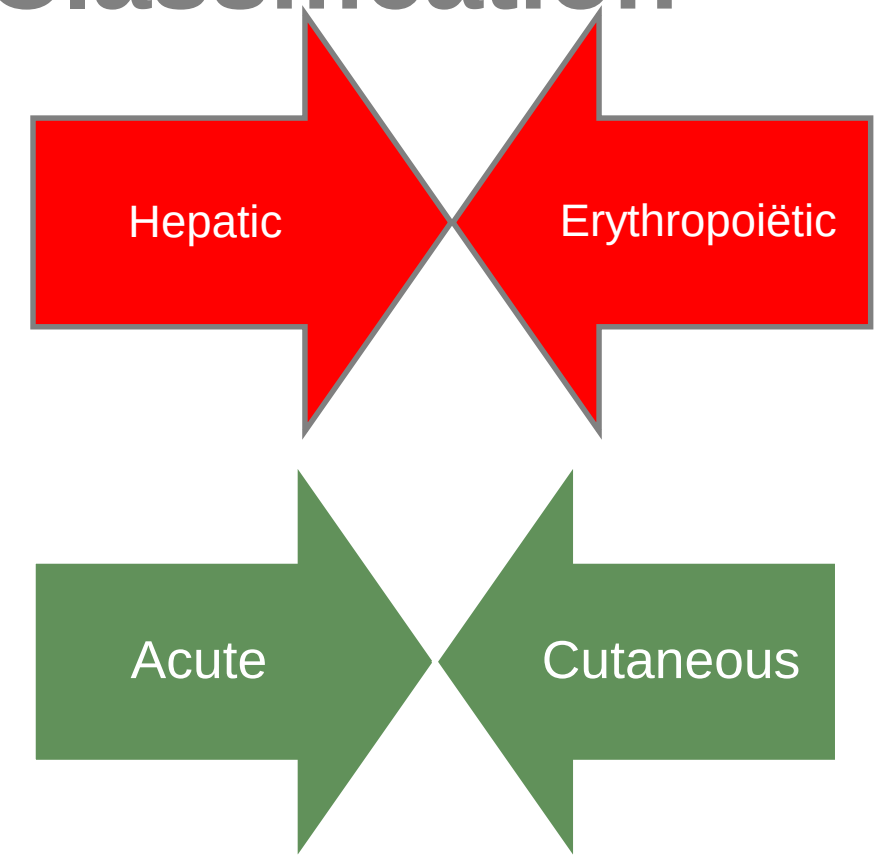
- **Classification**
  - Acute porphyria
  - Cutaneous porphyria
  - Rare recessive porphyrias
- Conclusion

2. Classification

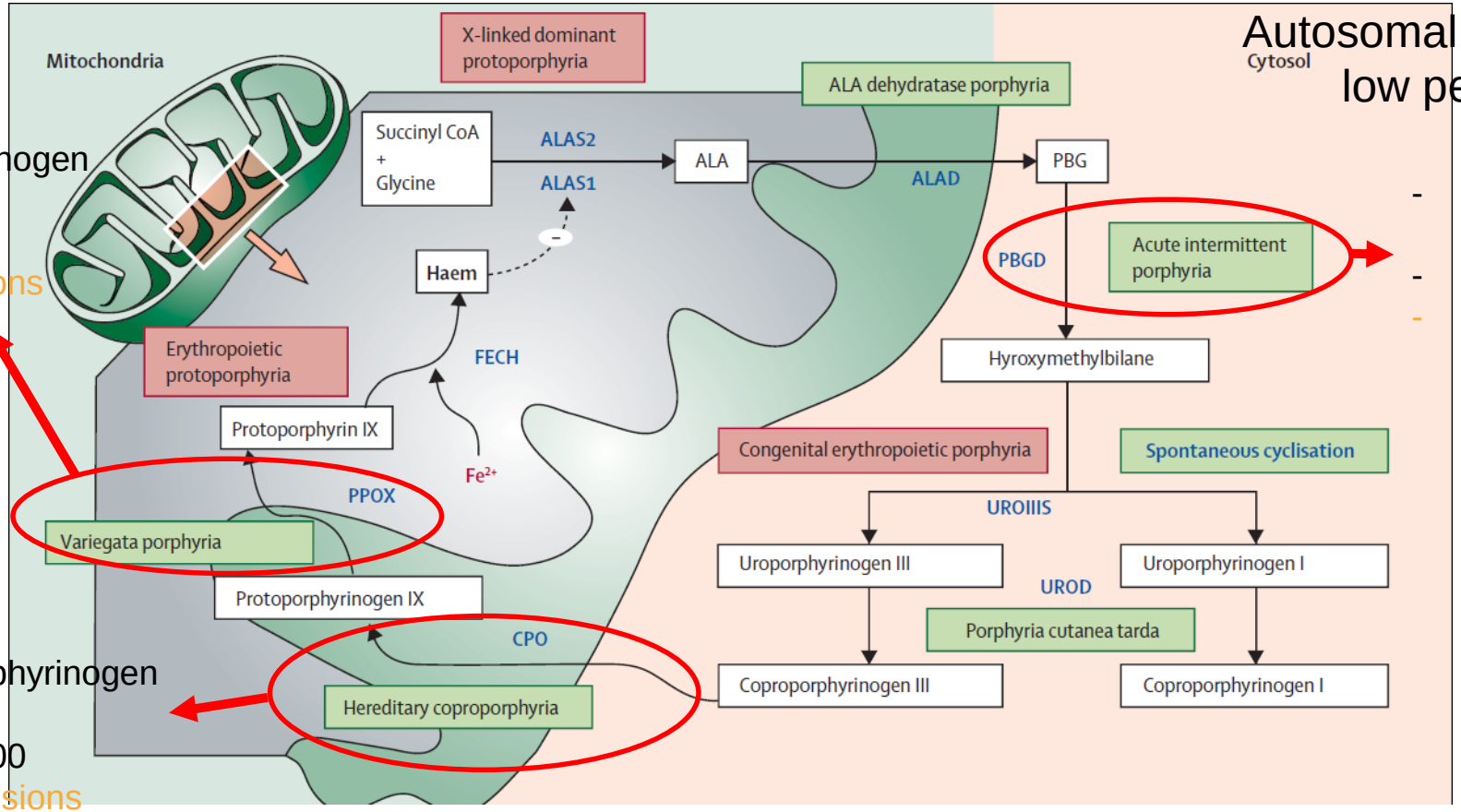


Acute porphyria	Cutaneous porphyria
- Acute intermittent porphyria (AIP) - ALA dehydratase porphryia (ADP)*	With blisters: **- Porphyria cutanea tarda (PCT)** - Congenital erythropoietic porphyria (CET)* - Hepatoerythropoietic porphyria (HEP)* Without blisters: **- Erythropoietic protoporphyria (EPP)** - X-linked dominant protoporphyria (XLDPP)

Combination
- Hereditary coproporphyria (HCP) - Variegate porphyria (VP)

* Very rare recessive form

A. Acute porphyrias



Autosomal dominant with low penetrance

- Protoporphyrinogen oxidase
- 1/150.000
- 80% skin lesions

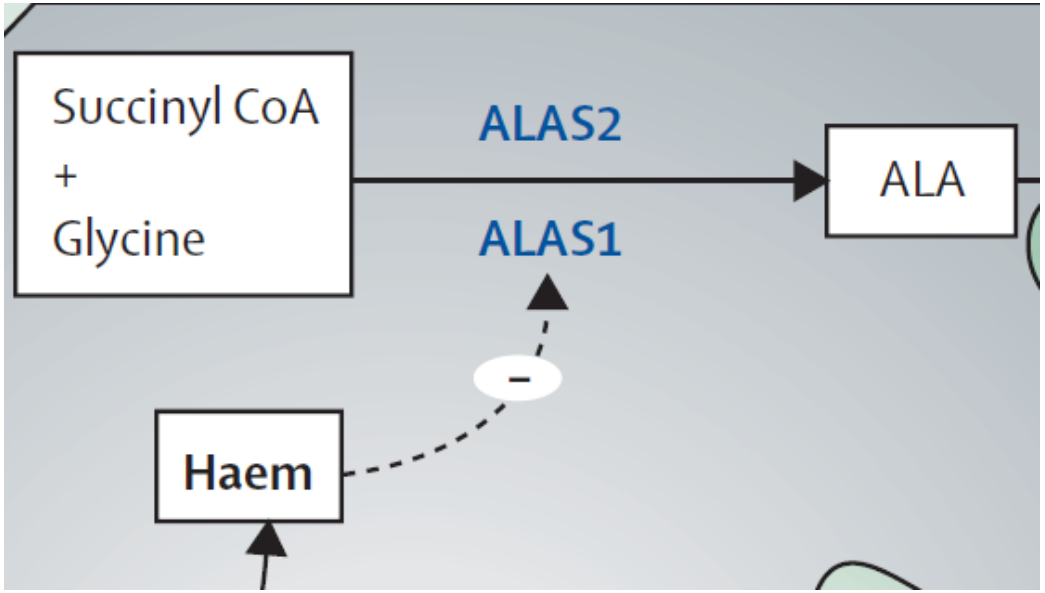
- porphobilinogen deaminase (PBGD)
- 1/75.000 (Sweden 1/1000)
- Never skin problems

- Coproporphyrinogen oxidase
- 2/1.000.000
- 5% skin lesions

Pathogenesis

- Overproduction of precursors in liver (PBG, ALA)

  -> neurotoxic



- Attacks provoked by events that
  - Induce ALAS1
  - Give rise increased breakdown of haem

- Events:
  - Hormonal fluctuations (menstrual cycle)
  - Not enough nutritional intake
  - Smoking
  - Alcohol
  - Porphyrinogen medication
    - CYP induction
  - Inflammation/infection
    - Induction of haem oxygenase 1 (acute phase reactant) -> breakdown of haem

Clinical presentation

- Women (80%) > men (20%)
- Between 20 and 40 yrs of age

- Acute attacks with neurovisceral pain
  - Visceral
    - Abdominal pain!
    - Pain in the back, in the area of the quadriceps (less frequently)
    - Nausea, vomiting, constipation
    - Normal clinical examination
    - Abdominal X-ray: sometimes ileus, distended colon

- Neurological
  - Mental disturbances
    - » Anxious, depressive, disoriented, hallucinations, paranoia, confusion, decreased level of consciousness
  - Neuropathy
    - » Motor neuropathy
    - » Pain and weakness in the muscles (proximal, arms > legs)
    - » If not recognized: tetraplegia with respiratory and bulbar paralysis
    - » Cave: porphyrinogenic drugs during attack
  - Pyramidal signs, ataxia, transient blindness (PRES)

- Increased sympathicus activity
  - Hypertension
  - Tachycardia
  - Sweating

- Electrolyte abnormalities (hyponatremia due to SIADH, hypomagnesemie)
  -> epilepsy

- Red or darkcolored urine

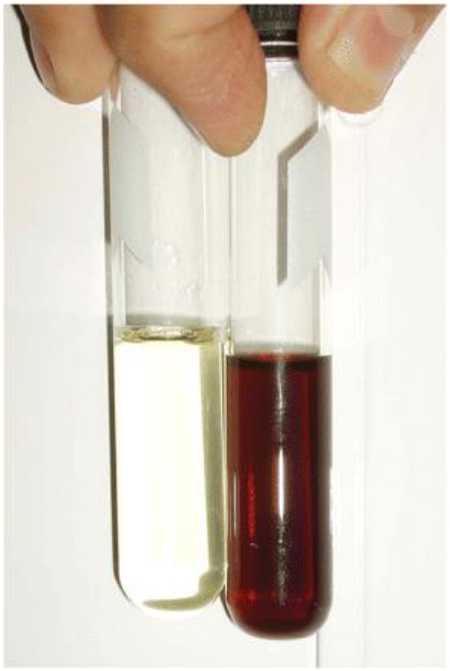
- Duration attack: 1 to 2 weeks
- Great majority of patients: only 1 to 3 attacks during life
- 10% frequent attacks

Diagnosis

- Samples (urine, plasma, faeces) should always be protected from light

- During attack
  - **Sample of urine**
    - Porphobilinogen (PBG)
      - » Semi-quantitative/qualitative
      - » Quantitative test
    - ALA
      - Lead intoxication and ALAD

-> increased in AIP, HCP and VP (concentrations highest in AIP)



- For further identification
  - Porphyrine measurement in
    - **Plasma**: fluorescence emission spectroscopy
      - VP: peak at 624-628 nm
      - HCP (en AIP): peak at 620 nm
    - **Faeces**
      - AIP: normal
      - VP: raised proto > copro
      - HCP: raised copro (III > I)
    - **Urine**
      - No substantial added value, sometimes subtle abnormalities in liver disease and bone marrow diseases
      - If normal and PBG/ALA also normal: acute porphyria excluded
      - Levels raised in AIP but to a much lesser extent than in PCT

- Voor confirmation: enzyme activity, mutation analysis

- During remission:
  - Normale porphyrin levels in urine, faeces and plasma
  - AIP: PBG and ALA raised during several months after the attack (sens 88%, spec 61%)
  - VP: Plasma fluorescence, peak at 624-628 nm (sens 60%, spec 100%)
  - HCP: ratio faecal copro isomer III/I > 2
  - Enzyme activity/DNA analysis

Treatment

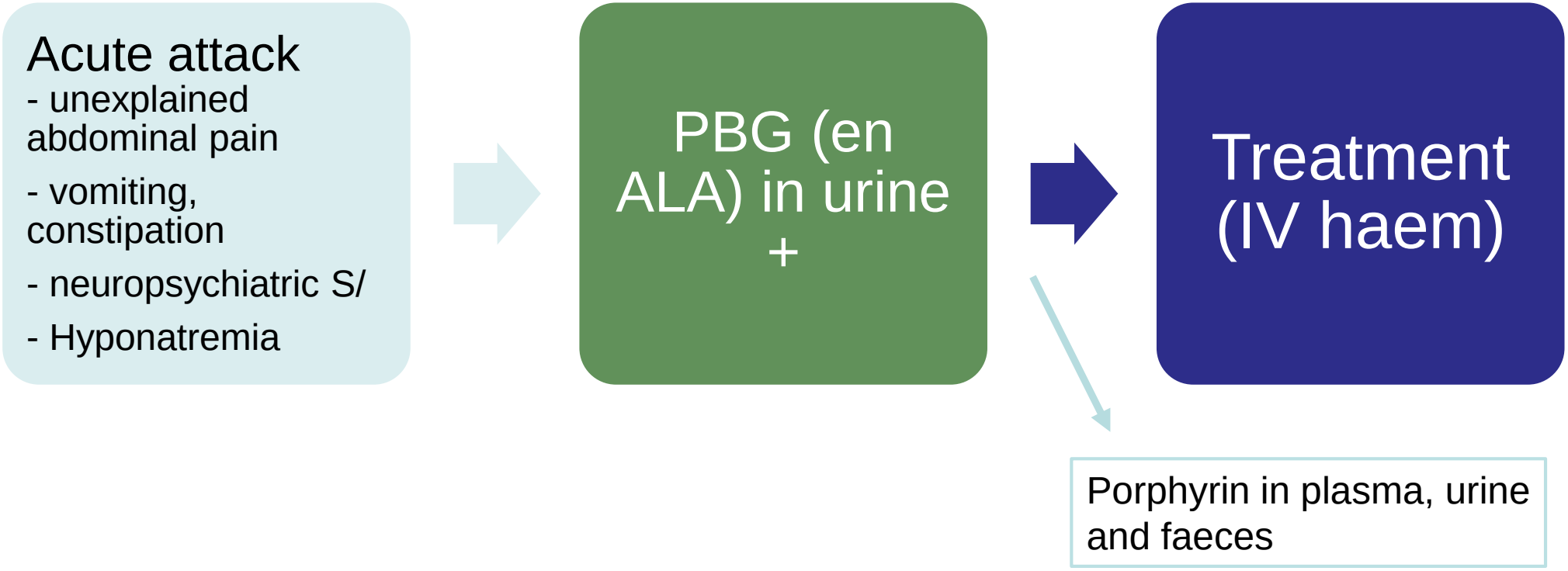
- Avoid precipitating agents
- Treat infection
- Symptomatic
  - Pain killers (opioids)
  - Anti-emetics
  - IV fluids (cave hyponatremia)
  - Anti-psychotics
  - In case of epilepsy: correction electrolytes, benzo's, gabapentin, clonazepam
  - Intensive care

Chart 2. Safe and contraindicated drugs for bearers of acute porphyria [4,5,12]

Contraindicated	Safe
Valproic acid	Acetaminofen
Àlcohol	Narcotic analgesics
Barbiturics	Aspirine
Calciu channel blockers	Atropine
Carbamazepin	Betablockers
Carisoprodol	Bromides
Clonazepam (high doses)	Cimetidine
Danazol	Clorpromazine
Diclofenaco	Diazepam
Ergots	Erythropoetine
Estrogen	Streptomycin
Phenytoin	Phenothyazines
Griseofulvin	Gabapentine
Pyrazenamide	Glucocorticoids
Progesterone	Chloral hydrate
Rifampicin	Serotonin reuptake inhibitors (anti-depressants)
Sulphonamides	Insulin
	Penicllin and derivatives
	Ranitidine

- Intravenous haem!
  - Inhibition of ALAS1
  - Human hemine (normosang)
  - 4 mg/kg for 3-4 days

- Repeated attacks
  - Consider maintenance treatment with haem
  - In severe cases: consider liver transplantation


Acute attack
- unexplained abdominal pain
- vomiting, constipation
- neuropsychiatric S/
- Hyponatremia
PBG (en ALA) in urine
+
Treatment (IV haem)
Porphyrin in plasma, urine and faeces

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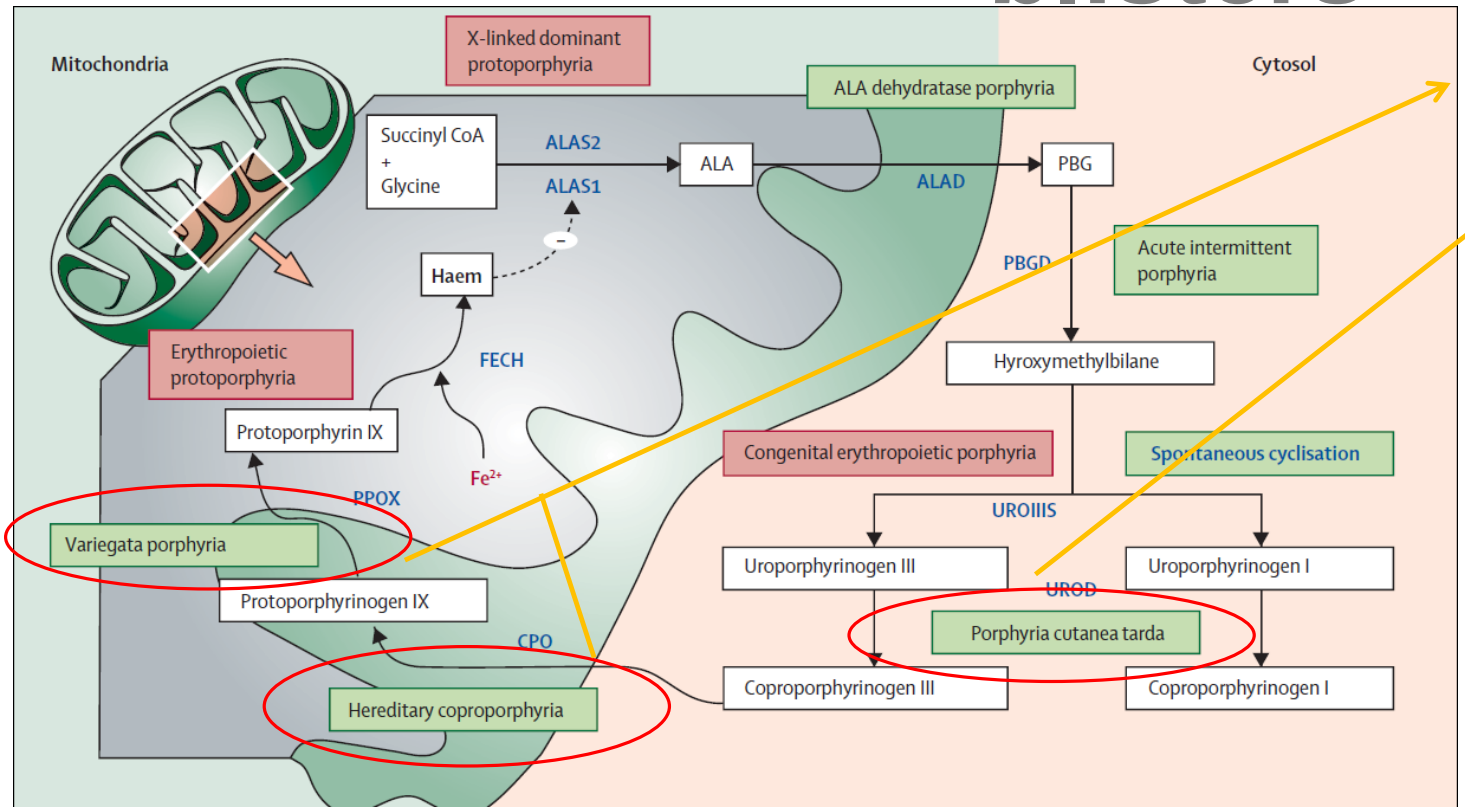
B. Cutaneous porphyrias with blisters



Porphyrins that build up in the skin

UV light

Excitation and oxidative stress

Blisters

Porphyria cutanea tarda

- By far most frequent porphyria (prevalence 1/5000 – 1/25000)

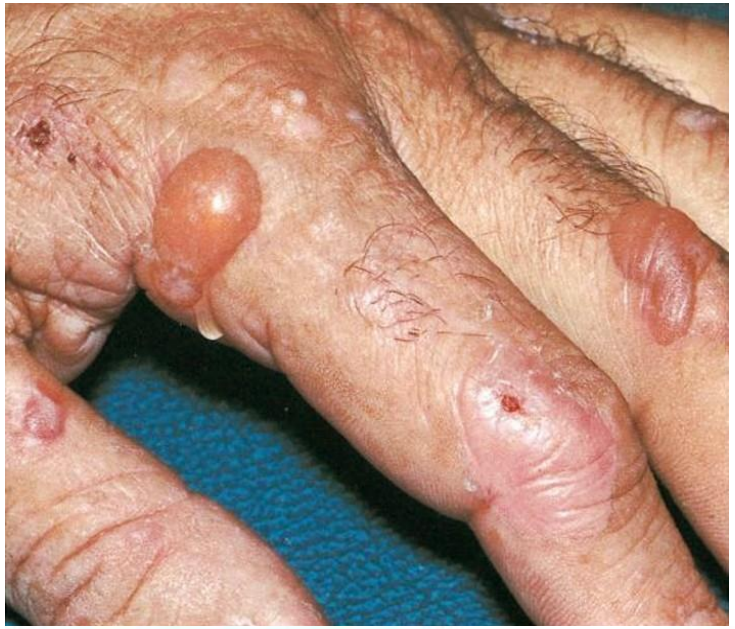
- 20% familial
  - Autosomal dominant with low penetrance
  - heterozygote -> 50% enzyme activity
  - Precipitating agents required for <20% enzyme activity and disease
  - Men = women
  - Early onset

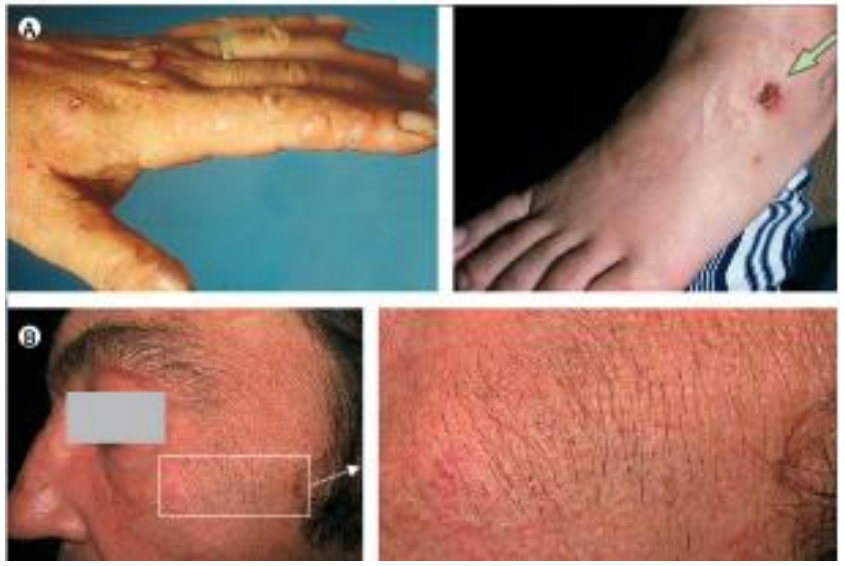
- 80% sporadic, acquired
  - No mutation, acquired inhibition of UROD
  - Men > women

- Pathogenesis PCT
  - Always a component of acquired inhibition of UROD in PCT
  - Risk factors
    - Iron deposition!
      - Hepatic siderosis in liver biopsy specimens
      - Increased iron parameters (transferrin saturation, iron, ferritin)
      - HFE mutation frequently found
      - Decreased expression of hepcidine
      - Ijzeropstapeling alleen = onvoldoende voor PCT
  - alcohol, smoking, Hep C, HIV, oestrogens, CNI
  - Uroporphyrinogen -> CYP1A2 induction in the presence of iron -> uroporphomethen -> inhibition of UROD

Clinical presentation

- Blisters in sun exposed areas
- Fragile skin
- Hyperpigmentation
- Milia (small white lesions)
- Hypertrichosis
- Rarely ocular signs (pain, photophobia)
- Liver function abnormalities
  - In association with alcohol
  - Cirrhosis and HCC

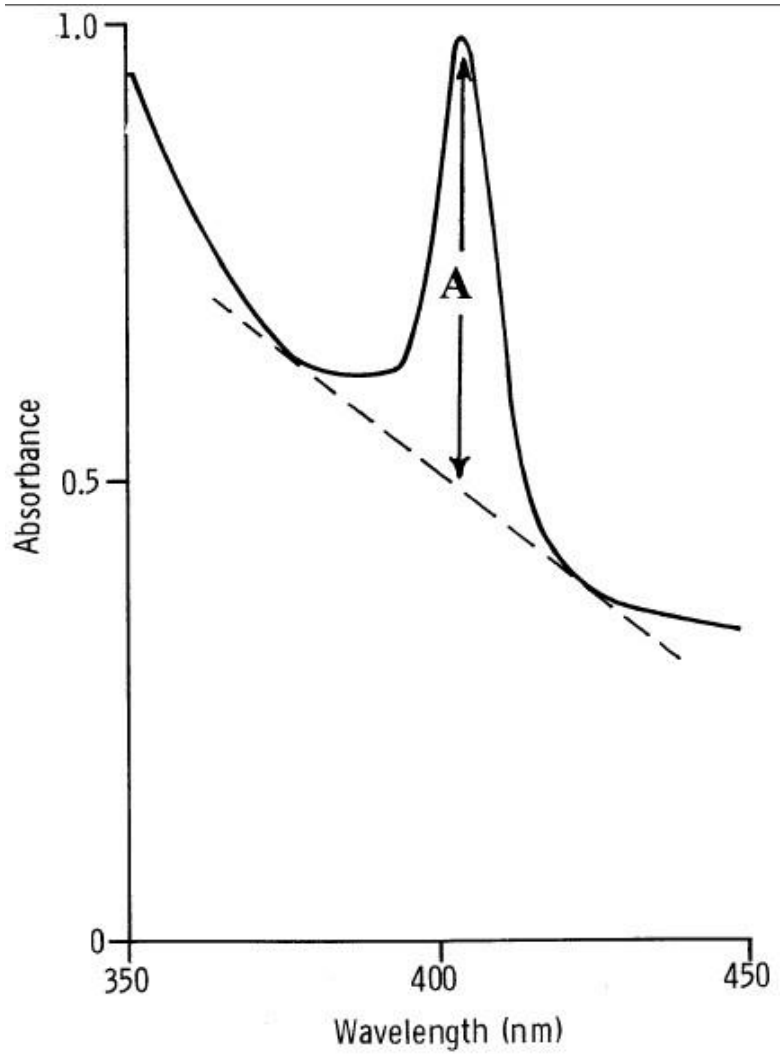




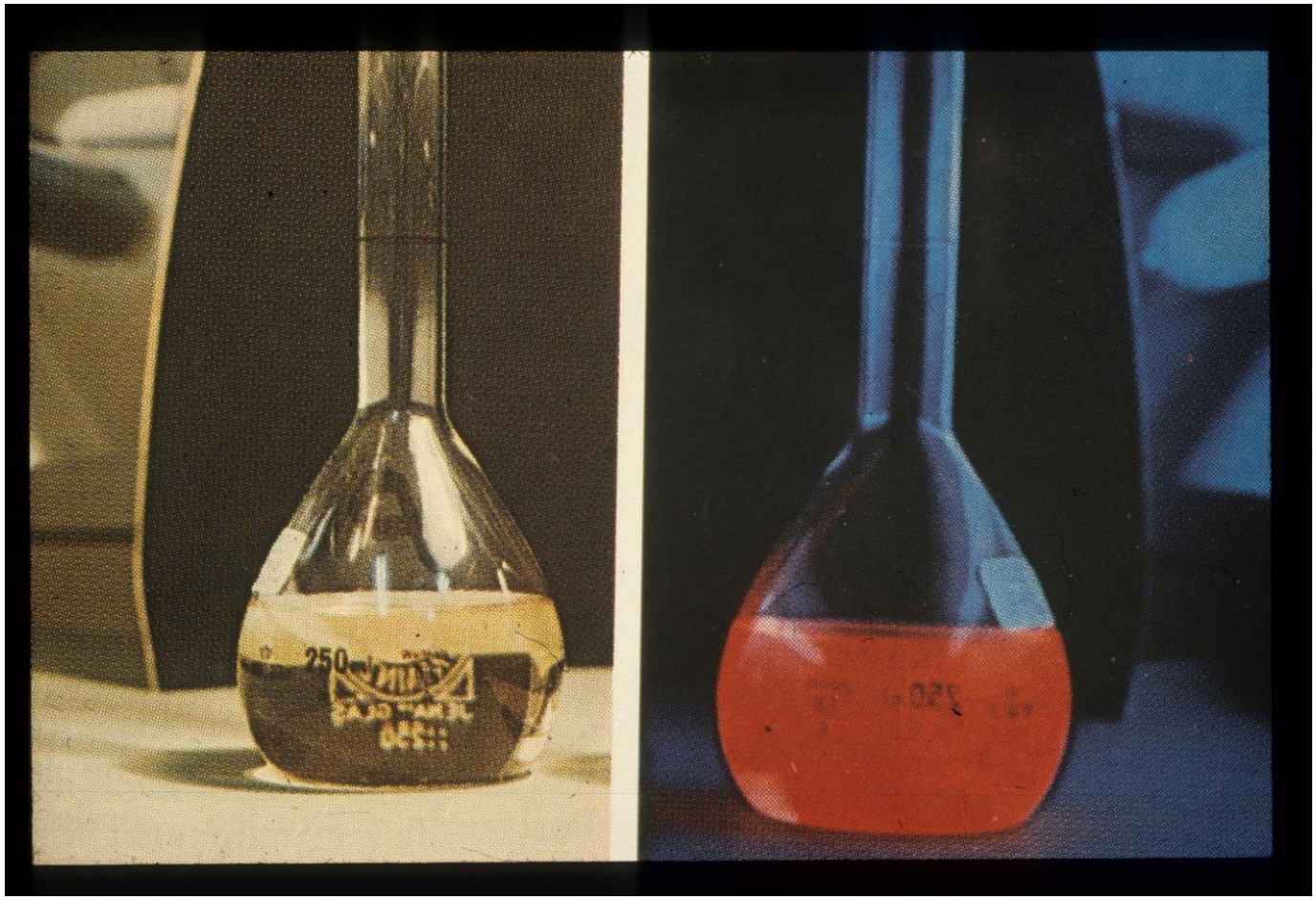
Diagnosis

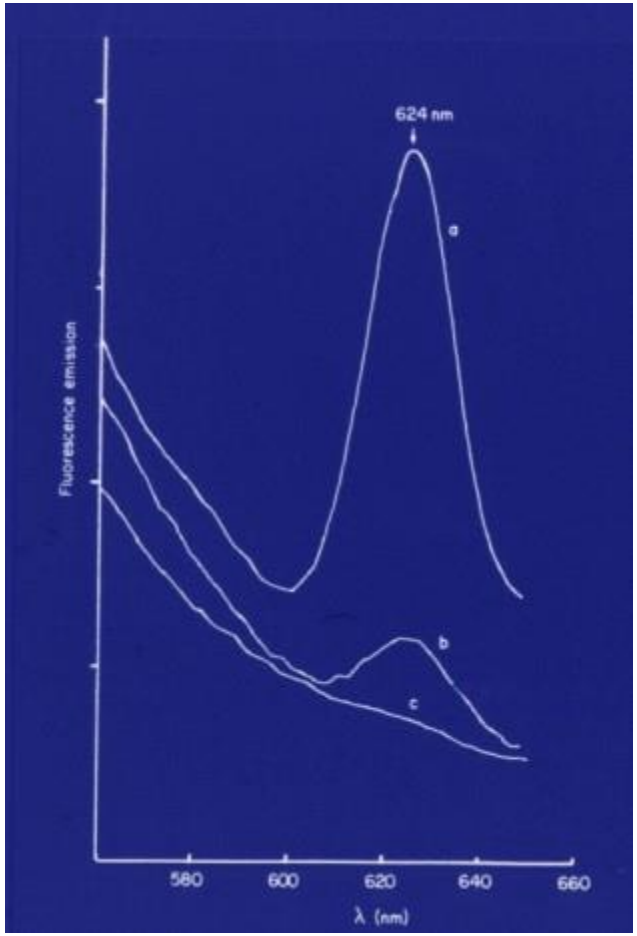
- Screening
  - Porphyrines in plasma
    - VP: peak at 624-628 nm - PCT: peak 620 nm
    - Chronically elevated
- Further differentiation
  - Urinary and faecal porphyrins
    - PCT
      - Urine: uroporphyrin, heptacarboxyl porphyrin
      - Faeces: isocoproporphyrins
- DNA-analysis, UROD activitity in RBC
  - In hereditary cases

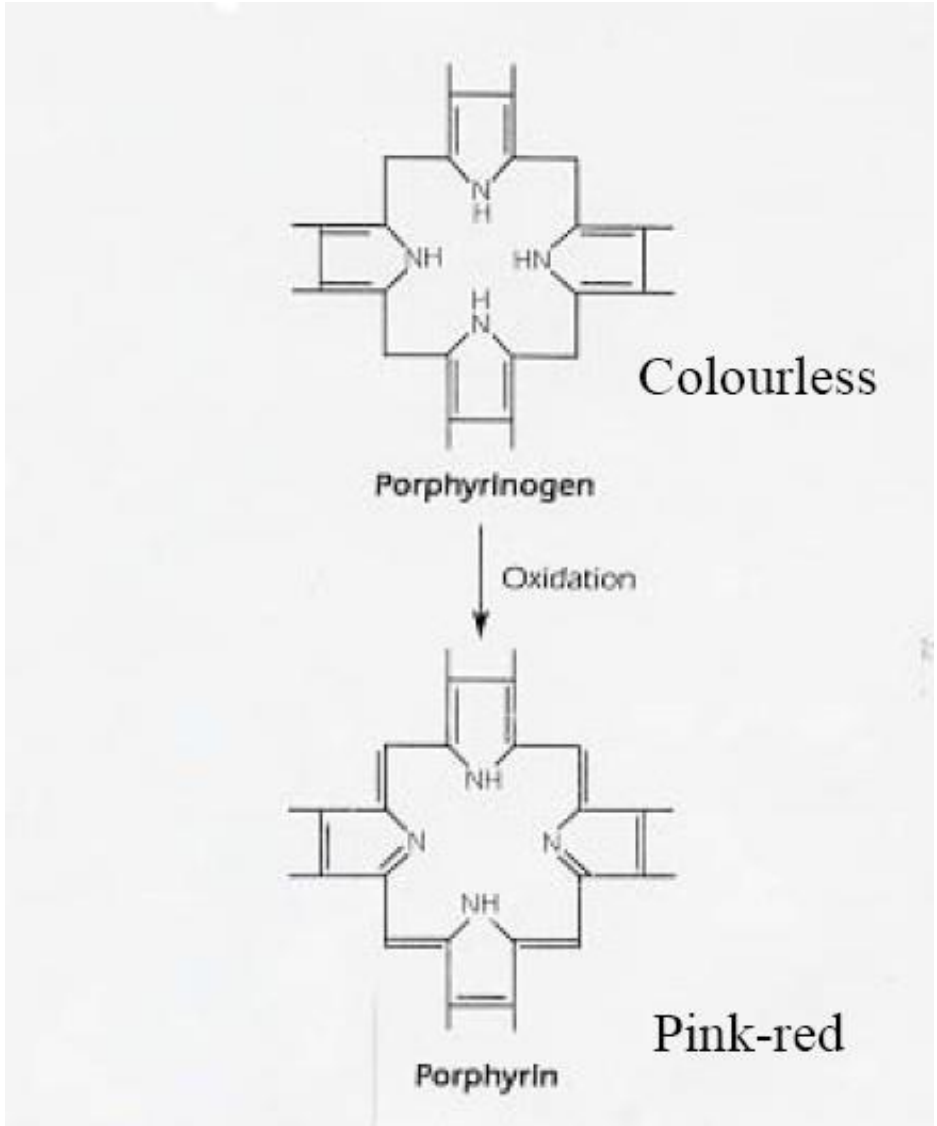
Porphyrins : light absorption



Porphyrines: fluorescence






Colourless
Porphyrinogen
Oxidation
Pink-red
Porphyrin

Treatment

- Protection from sunlight
- Avoid precipitating factors (alcohol, roken, E, ...)
- <u>In PCT:</u>
  - *Chloroquine* 100-200 mg 2x/week
    - Complex with porphyrins -> increased excretion in urine
  - *Phlebotomy*
    - 300-500 cc weekly until transferrin sat < 16%, normal ferritin
    - Treatment of choice in hemochromatosis
  - Combination
  - Monitoring:
    - plasma and urinary porphyrin concentration: should normalize after 9 months

Erosive photodermatitis

- Blisters
- Fragile skin
- hypertrichosis

Porphyrines in plasma

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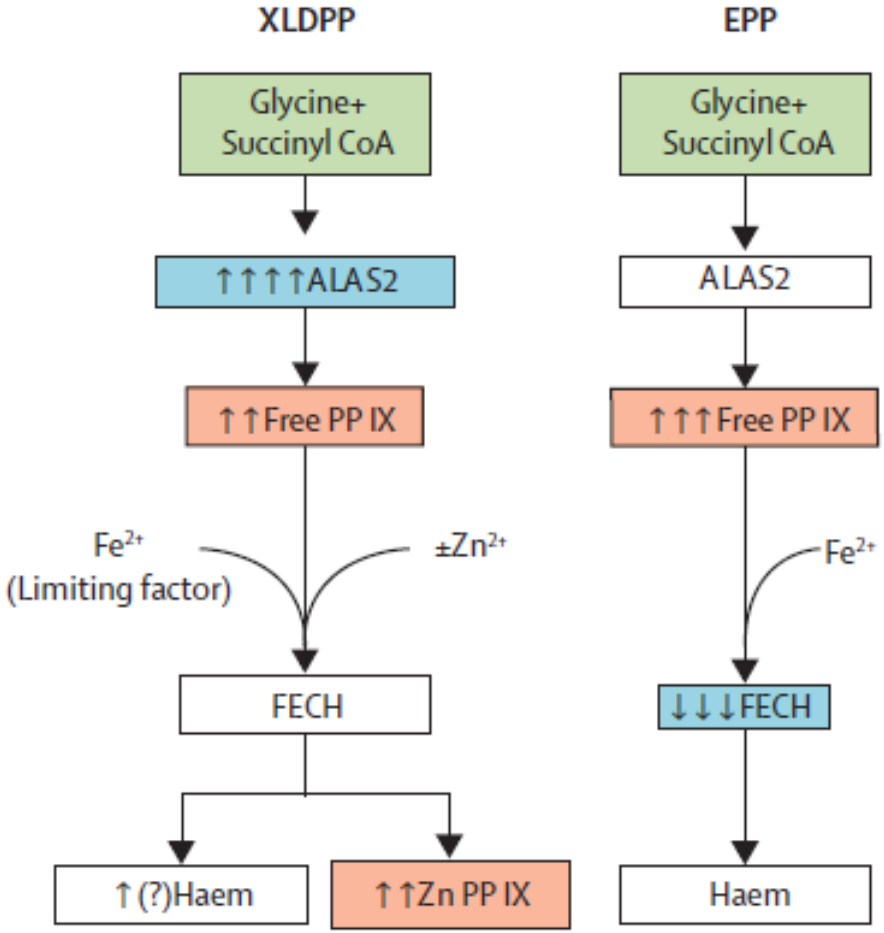
C. Acute painful photosensitive porphyria

- Erythropoietic protoporphyria
  - 1/75.000 – 1/200.000
  - Ferrochelatase deficiency (< 35%)
  - Inherited
    - Pseudodominant:
      - 1 mutant allel (no activity) – 1 polymorph allel with reduced activity
    - Homo- or compound heterozygote: severe disease with liver involvement
  - Acquired
    - Myelodysplasia and myeloprolipherative disorders
- X-linked protoporphyria (XLDPP)
  - Men > women
  - Increase ALAS2 activity
  - Gain of function mutation
  - Liver involvement

Pathogenesis

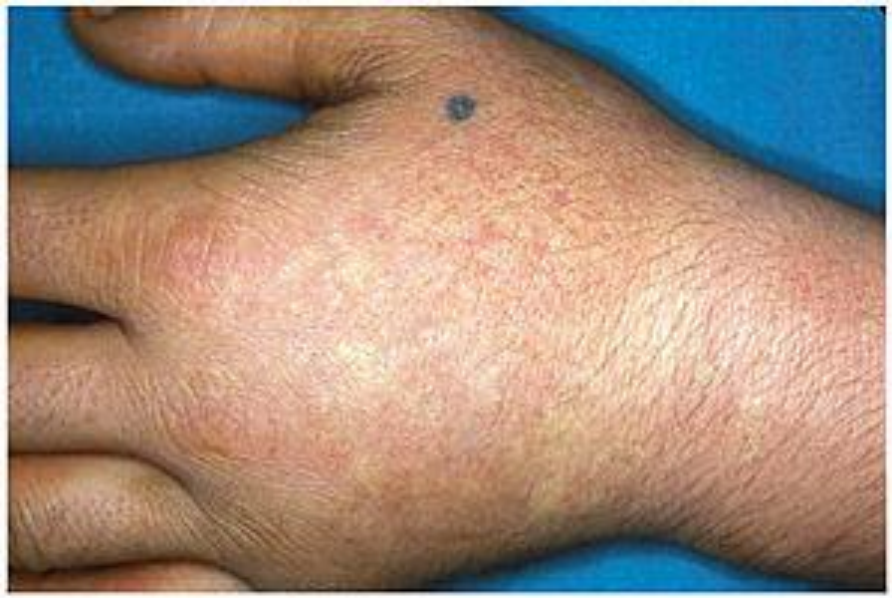


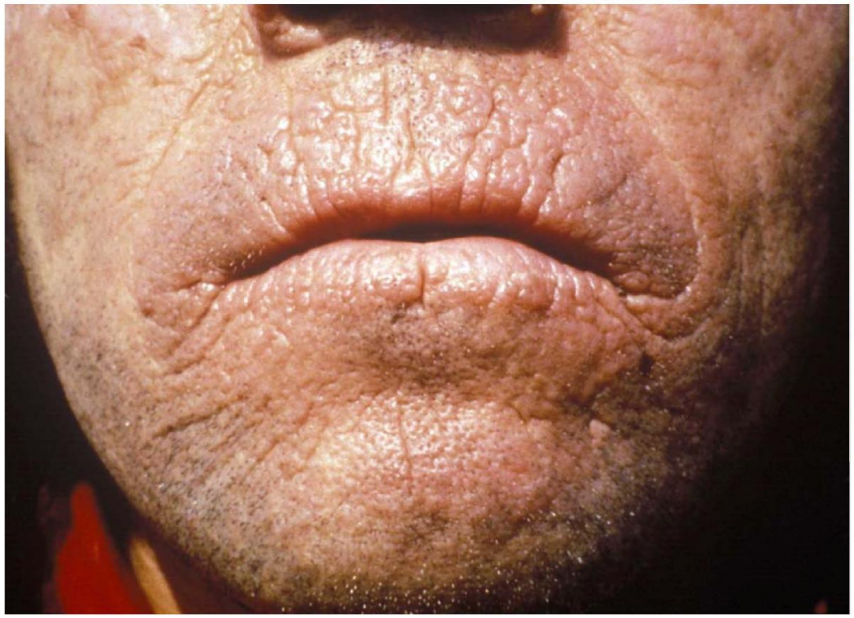
Protoporphyrin accumulation in RBC, skin, liver, bile and faeces

-> painful photosensitivity and to a lesser extent cholestatic liver disease

Clinical presentation

- **Acute photosensitivity**
  - Begins in childhood
  - Burning painful sensation after a few minutes of sun exposure
  - Relief with cold water
  - Edema and erythema
  - Chronic
    - Skin tighter
    - Scars in the face





- **Liver abnormalities**
  - In 10-20% of cases
  - Protoporphyrin gall stones
  - Cholestatic liver failure in 2%
    - Accumulation of protoporphyrin in hepatocytes/bile canaliculi

Diagnosis

- Protoporphyrin is lipidsoluble
  -> no urinary excretion
- Increased concentration free protoporphyrin in RBC and in plasma (peak at 634 nm)
- EPP
  - Enzyme activity of FECH < 35%
  - DNA-analysis
- XLDPP
  - Increased free and zinc protoporphyrin
  - Normal FECH activity
  - DNA-analysis

Treatment

- Protection from the sun
- UVB fototherapy
- Afamelanotide (alfa-MSH)
  -> melanin formation
- Beta-carotene (75-200 mg/day)

- In case of liver abnormalities
  - Cholestyramin (?)
  - Active coal (?)
  - Liver failure -> liverTx (combination with stem cellTx?)
    - Cave light exposition during surgery

Acute painful photosensitivity

Burning pain and itching in sunexposed areas

Protoporphyrin IX in RBC

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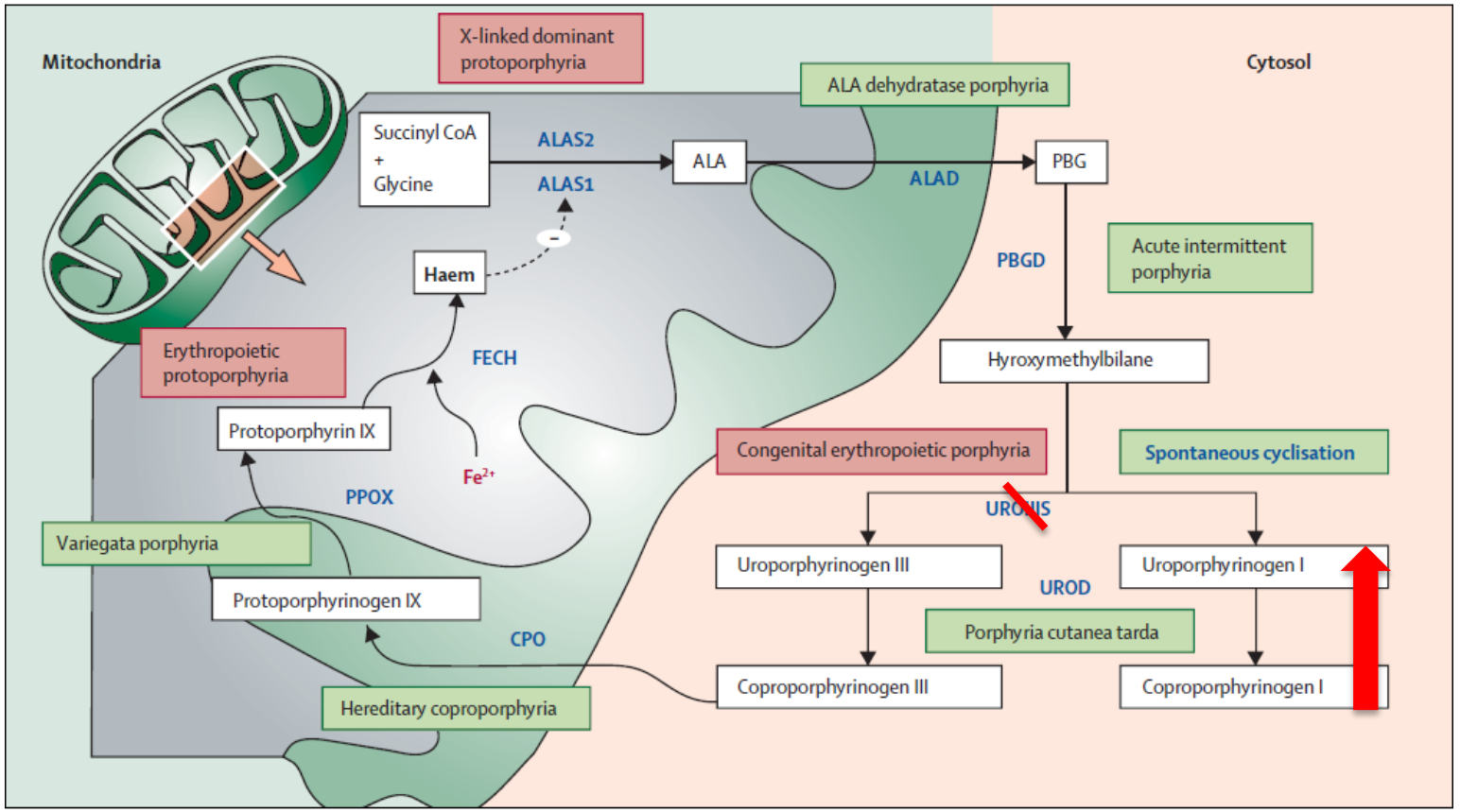
Congenital erythropoietic porphyria (Gunther's disease)



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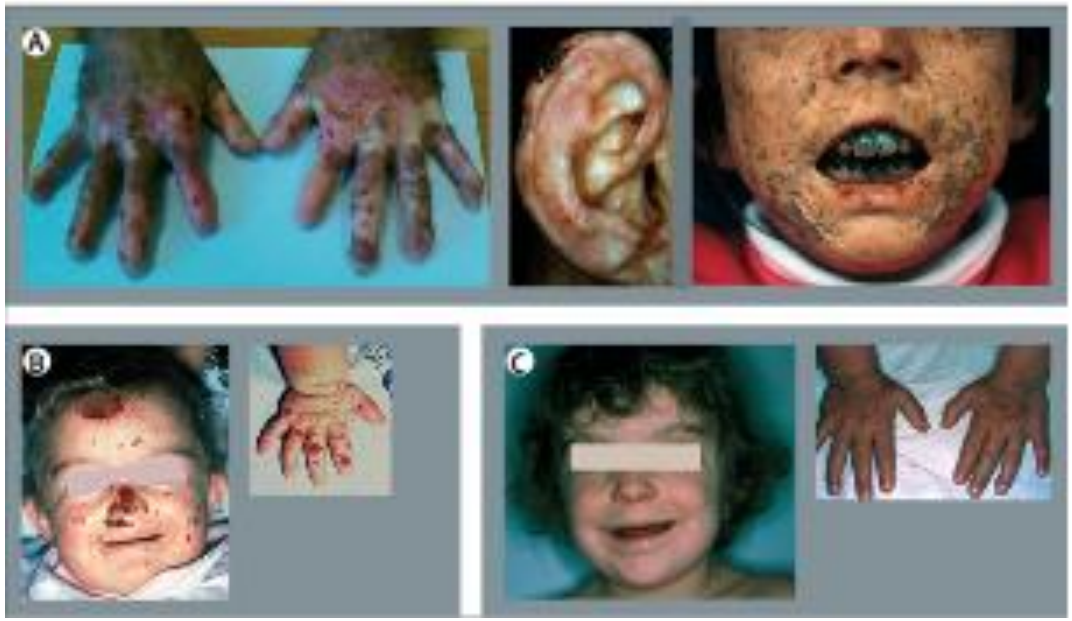
Congenital erythropoietic porphyria (Gunther's disease)

- 1/2.000.000

- **Presentation**
  - Very severe photosensitivity
    -> bullae, scars
    -> ulcerative keratitis
  - Erythodontia
  - Osteodystrophy
  - Red urine
  - Haemolysis and big spleen



- **R/**
  - Sun protection
  - Transfusions, splenectomy
  - Bone marrow transplantation

Porphyria

- Introduction

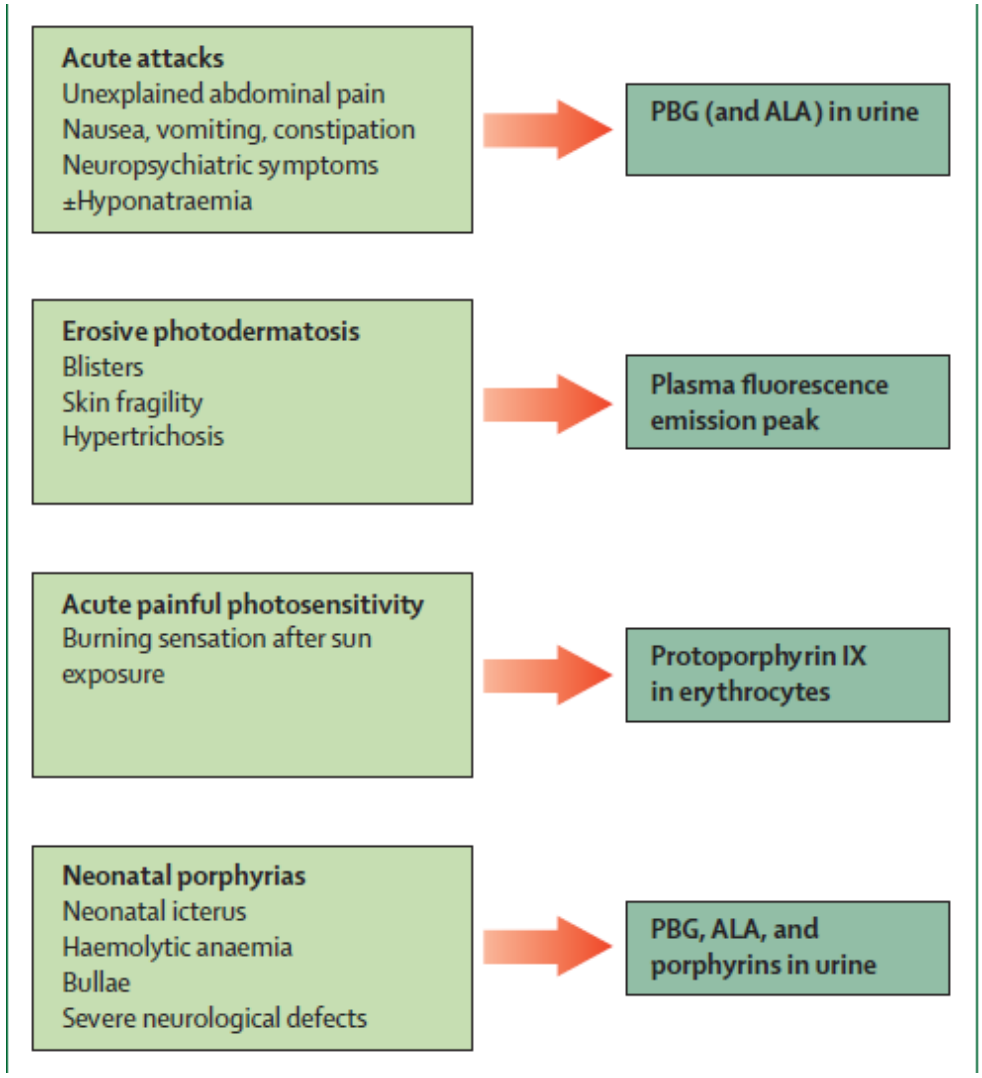
- Classification
  - Acute porphyria
  - Cutaneous porphyria
  - Rare recessive porphyrias

- **Conclusion**

Conclusions

- Deficiency in one of the eight enzymes required for haem synthesis

- Classification
  - **Acute porphyrias**
    - Neurovisceral symptoms
    - *Acute intermittent porphyria*
  - **Cutaneous porphyrias**
    - With blisters: *porfyria cutanea tarda*
    - Without blisters: *erythropoietic porphyria*
  - Rare recessive other entities


Acute attacks
Unexplained abdominal pain
Nausea, vomiting, constipation
Neuropsychiatric symptoms
±Hyponatraemia
PBG (and ALA) in urine
Erosive photodermatosis
Blisters
Skin fragility
Hypertrichosis
Plasma fluorescence emission peak
Acute painful photosensitivity
Burning sensation after sun exposure
Protoporphyrin IX in erythrocytes
Neonatal porphyrias
Neonatal icterus
Haemolytic anaemia
Bullae
Severe neurological defects
PBG, ALA, and porphyrins in urine

- If you want to know more on inborn errors of metabolism
    - Saudubray et al Inborn metabolic disorders
- Previous summer school in Brighton
    - Aunt Minnie’s popquiz