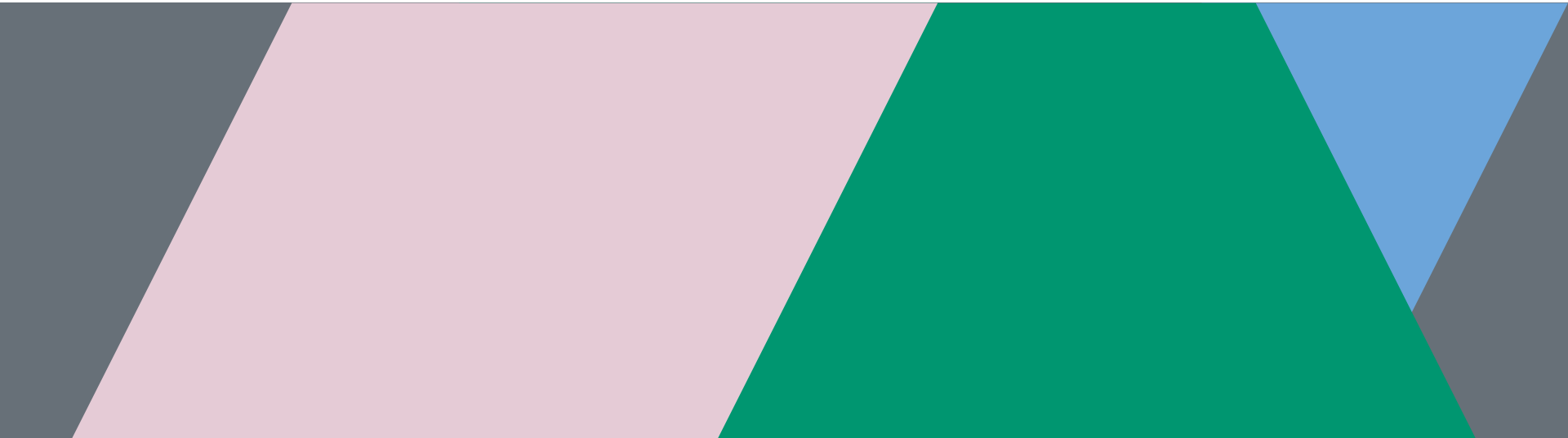
INSELGRUPPE

Bible Class – Porphyria

24.8.2022 Niklas Krupka



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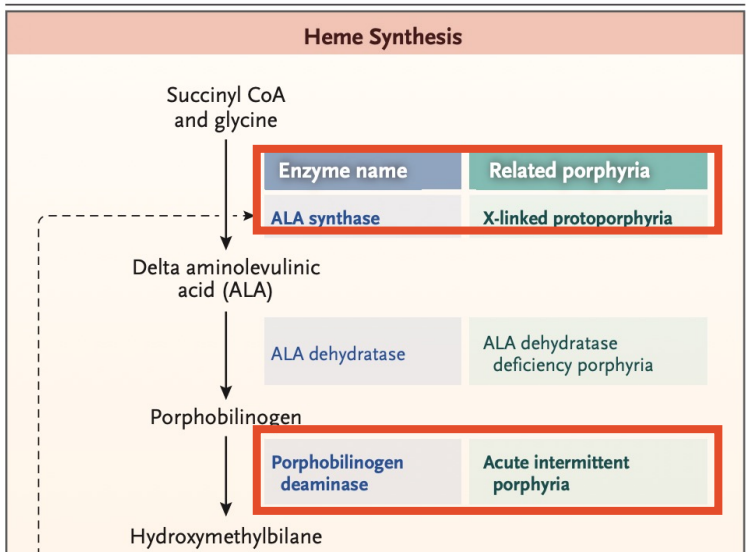
Background

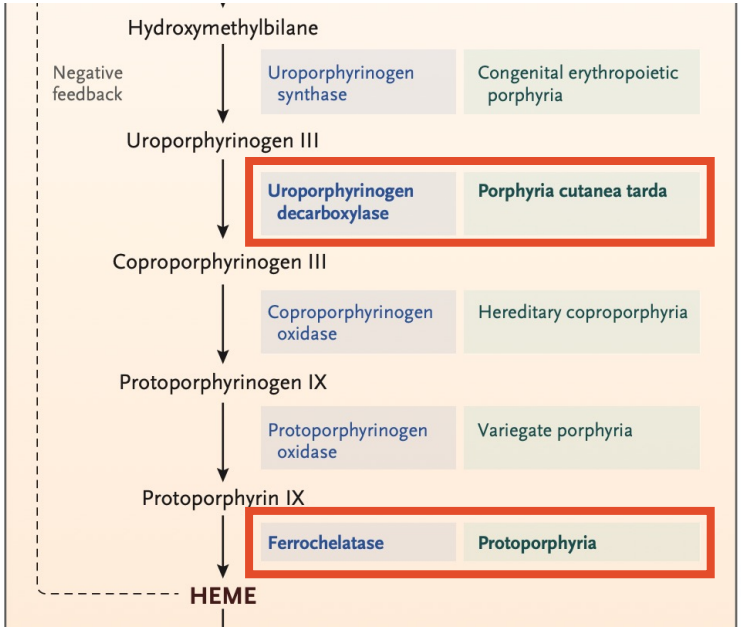
Porphyria

- Porphyria = disorder of **heme** synthesis
- Each porphyria involves a distinct defect of a heme pathway enzyme
- Symptoms arise due to accumulation of pathway precursors

Acute hepatic porphyrias	(Chronic) photocutaneous porphyrias

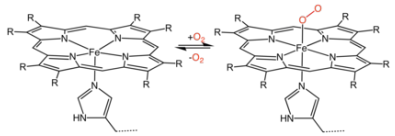
Heme synthesis





relatively common

rest: rare to very rare



Genetics

- Most porphyria patients are heterozygous for mutations in genes associated with heme synthesis
- Most porphyrias are autosomal dominant disorders
- Penetrance is very variable (i.e. other genetic/environmental factors play a role)

Table 2. Protein and Genetic Features and Prevalence of Porphyrias

Porphyria	Deficient enzyme	Gene locus	No. of mutations reported	No. diagnosed [a,b]	Prevalence[c] reported	OMIM no.
ALADP	ALA-dehydratase	9q33.1	12	3	Rare[d,e]	612740
AIP	PBG deaminase	11q23.3	390	878	5.9[f]	176000
CEP	Uroporphyrinogen III synthase	10q25.2-10q26.3	48	35	Rare[e,g]	263700
PCT, HEP[h]	Uroporphyrinogen decarboxylase	1p34	121	3131	21[i]	176100
HCP	Coproporphyrinogen oxidase	3q12	50[i]	78	0.9[i]	121300
VP[k]	Protoporphyrinogen oxidase	1q22	174	133	3.2	176200
EPP	Ferrochelatase	18q21.3	189	289	9.2[i]	177000
XLP	ALA synthase 2	Xp11.21	4	3	Rare[e]	300752

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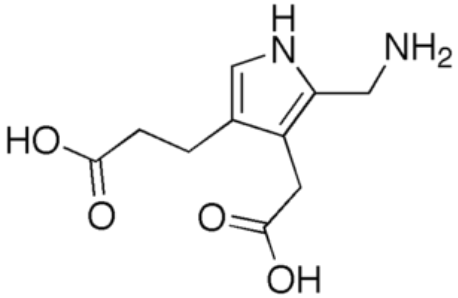
Acute intermittent porphyria (AIP)

Acute intermittent porphyria

- Partial deficiency in porphobilinogen desaminase
- Accumulation of **porphobilinogen** and delta ALA
- Prevalence of mutations 1:2000, penetrance only 10%
- Age peak 30–35y, F>M
- Important triggers: caloric deficit, medications



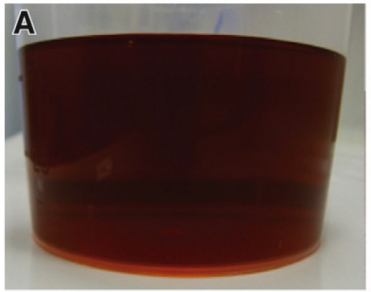
Acute intermittent porphyria – Symptoms

Acute attacks of

- **Abdominal pain** (severe, poorly localized, often involves back/legs)
- **Tachycardia**
- **Vomiting**
- **Neurologic signs** (fatigue, motor neuropathy, seizures, rarely psychosis)

Analgesic agents provide no relief

Lack of objective findings
(unreliable: dark urine)



Acute intermittent porphyria – Diagnosis

Highly elevated **porphobilinogen** in plasma or urine (random sample)

Table 2. Heme Pathway Intermediates in the Diagnosis of Porphyria.*

Pathway Intermediate	Reference Range	Asymptomatic Acute Intermittent Porphyria	Acute Intermittent Porphyria during Attack	Porphyria Cutanea Tarda without Symptoms (Treated)	Active (Untreated) Porphyria Cutanea Tarda	Protoporphyria
Porphobilinogen in urine (mg/g of creatinine)	0–2	1–10†	20–300	<2	<4	—
Uroporphyrin in urine (μg/g of creatinine)	0–30	<30	20–200	30–300	>500	—
Protoporphyrin in blood (μg/dl)	0–80	—	—	—	—	>400

Sometimes: Severe hyponatremia (ADH↑)

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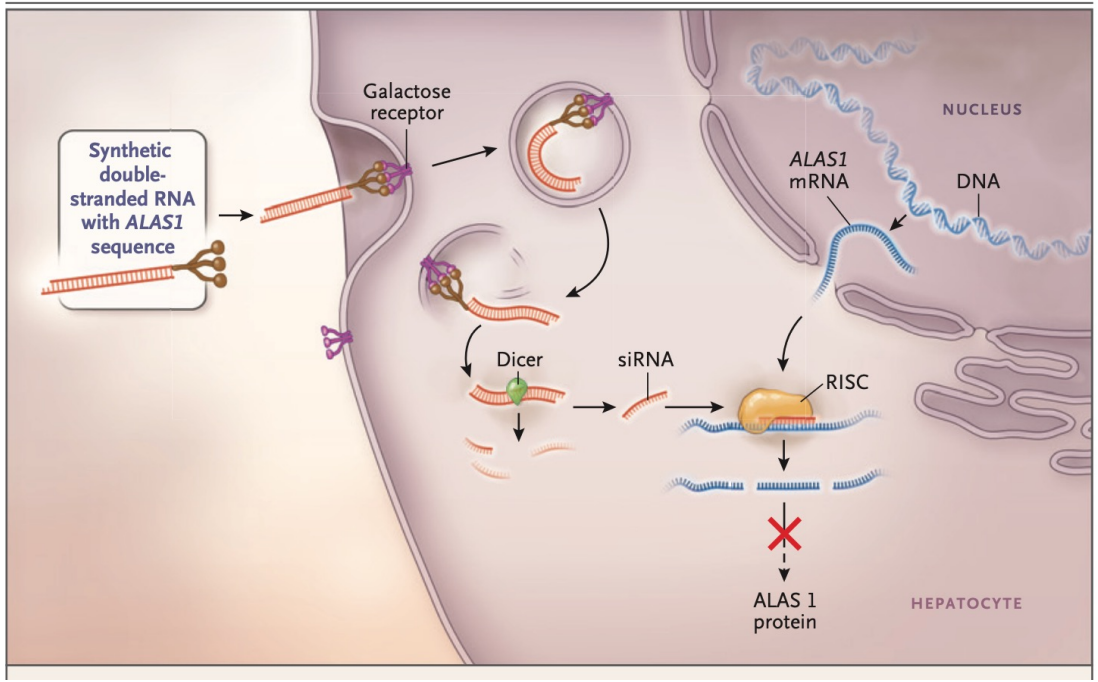
Acute intermittent porphyria – Treatment

- Avoid trigger medications
- Fluids (Glucose/NaCl), caloric support
- Symptomatic treatment (antiemetics)
- Specific treatment: intravenous heme (Normosang)

Table 3. Safety of Medications in Patients with Acute Porphyria.*

Medication	Safety
Anticonvulsants	
Phenytoin	Unsafe
Barbiturates (all types)	Unsafe
Valproic acid	Unsafe
Carbamazepine	Unsafe
Primidone	Unsafe
Clonazepam	Possibly unsafe
Lorazepam	Probably safe
Gabapentin	Probably safe
Magnesium sulfate	Probably safe
Propofol	Probably safe
Ketamine	Possibly unsafe
Bromides	Probably safe
Other medications	
Oral contraceptives	Unsafe
Progestins	Unsafe
Carisoprodol	Unsafe
Spironolactone	Unsafe
Furosemide	Probably safe
Imipramine	Possibly unsafe
Chlorpromazine	Probably safe
Ibuprofen	Probably safe
Opioids	Probably safe
Diphenhydramine	Probably safe
Lithium	Probably safe
Meclizine	Probably safe
Aminoglycoside antibiotics	Probably safe
Penicillins	Probably safe
Sulfa antibiotics	Possibly unsafe
Erythromycin	Possibly unsafe
Fluconazole	Possibly unsafe
Nitrofurantoin	Possibly unsafe
Rifampicin	Possibly unsafe
Warfarin	Probably safe

Acute intermittent porphyria – Future outlook



Acute intermittent porphyria – Prognosis

- Abdominal symptoms usually resolve over a few days
- Motor defects remain longer and sometimes do not resolve
- In case of recurrent attacks: prophylactic heme, liver transplantation (rare)

- Increased risk of
  - chronic liver disease
  - chronic kidney disease
  - HCC (indication for screening)

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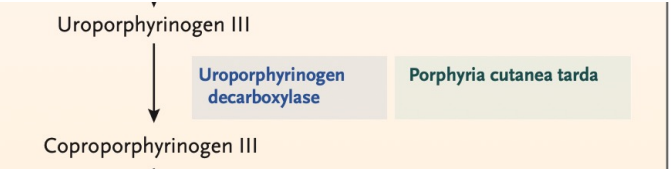
Porphyria cutanea tarda (PCT)

Porphyria cutanea tarda



- Most prevalent porphyria (1:2000 to 1:1000)
- Partial insufficiency of uroporphyrinogen decarboxylase (not necessary mutation)
- Usually > 1 risk factor
- Onset usually >40y
- Pathogenesis involves **iron overload**

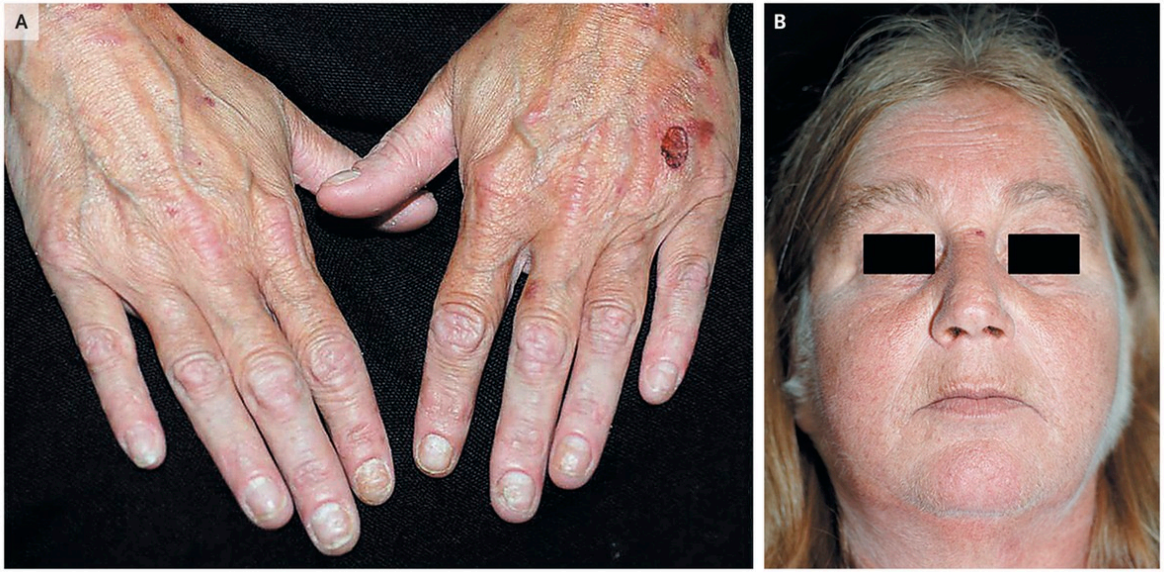
Table 4. Susceptibility Factors in Patients with Porphyria Cutanea Tarda.*

Factor	Prevalence *percent*
Acquired factors	
Hepatitis C virus infection	69
Alcohol consumption	87
Tobacco use	81
Estrogen use (in female patients)	66
Human immunodeficiency virus infection	13
Genetic factors	
Uroporphyrinogen decarboxylase mutation	17
Genetic hemochromatosis	53
C282Y/C282Y genotype	6
C282Y/H63D genotype	8
C282Y/- and H63D/- genotypes	39

* Data are from Jalil et al.[41]

Porphyria cutanea tarda – Symptoms

- **Photosensitivity** (excitation of porphyrins by blue light)
- Hypertrichosis



N Engl J Med 2013; 369:1356

Porphyria cutanea tarda – Diagnosis

- **Urine or plasma porphyrin profile**

Table 2. Heme Pathway Intermediates in the Diagnosis of Porphyria.*

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Porphyria cutanea tarda – Treatment

- **Phlebotomy**
- In case of anemia: iron chelator (deferasirox)
- Alternative: (hydroxy-)chloroquine (mobilize intrahepatic porphyrins)

- Restriction of alcohol, tobacco, oral contraceptives
- Treatment of HCV infection

→ Leads to remission in >90% of cases

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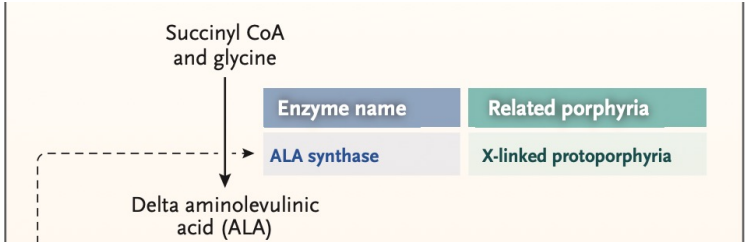
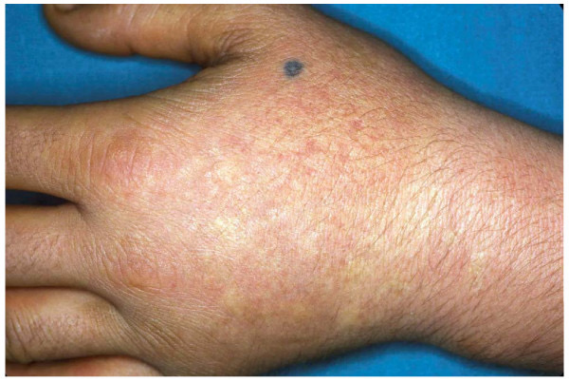
Protoporphyria

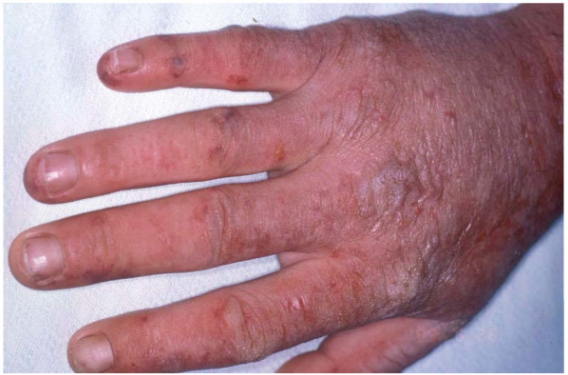
Protoporphyria

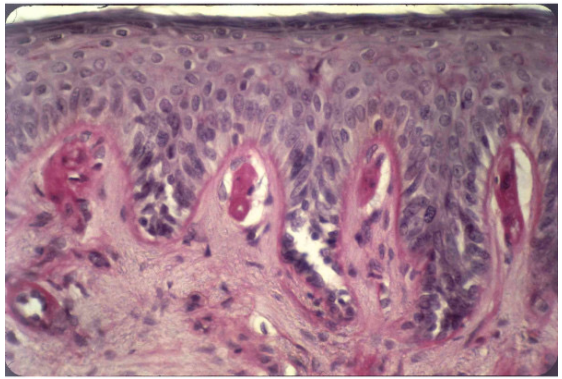
- Overproduction of protoporphyrin in the bone marrow
- Two forms **X-linked protoporphyria** vs **ferrochelatase deficiency**
- Manifestation usually in early childhood



Protoporphyria – Signs and symptoms







In 5% of patients: liver disease

Protoporphyria – Diagnosis

- **Whole blood protoporphyrin**

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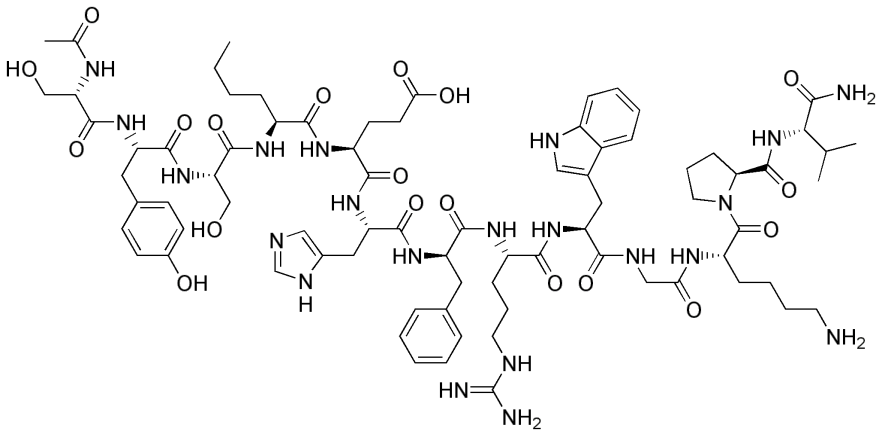
Protoporphyria – Treatment

- **Avoidance of sun exposure**
- Afamelanotid (analogue of α-MSH)



Summary

- **Porphyrias are relatively rare, but frequently missed**

Table 4. Clinical and Biochemical Features of Porphyrias

AHP (Patients after puberty)	PCT (Adult patients Aged >18 y)	Protoporphyrias (Children or adolescents)
Unexplained gastrointestinal complaints (colic, vomiting, subileus) Neurologic symptoms (paresthesia, seizures, paresis) Mental abnormalities (depression, anxiety, hallucination) Tachycardia, hypertension Red-colored urine without erythrocytes or hemoglobin Serum hyponatremia	Blister-forming dermatosis on light-exposed skin areas Increased skin vulnerability Hyper- and hypopigmentation on light-exposed skin Hypertrichosis of cheeks, temples, and the eyebrows, often associated with: Iron overload HCV infection HIV infection Alcohol consumption Hormone (replacement) therapy Toxic agents (eg, hexachlorobenzene)	Burning pain Erythema/redness on light-exposed skin areas Angioedema-like swelling on the face, on the back of the hands and on the forearms Often microcytic anemia Possible family history
Key biochemical features		
>4-fold elevated ALA and PBG in urine	ALA and PBG in urine normal, elevated total porphyrins in urine with uroporphyrin > coproporphyrin	ALA and PBG in urine normal, metal-free erythrocyte protoporphyrin increased in blood