The Porphyrias

Disorders of Heme Synthesis

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معرفی بیمار

- خانم ۵۱ ساله
- سابقه بستری های مکرر به دلیل درد شکم:

➢ حملات درد شکم و تنگی نفس با تشخیص آسم تحت درمان با کورتون قرار گرفته

➢ حملات درد شکم واستفراغ با تشخیص گاستریت تحت درمان قرار گرفته

آندوسکوپی و کولونوسکوپی نرمال

جراحی شکم و خارج کردن رحم

➢ ضایعات کهیری

➢ با تشخیص اختلالات سایکولوژی تحت درمان داروهای روانپزشکی قرار گرفته

			Children: (Up to 15 years) :180-1200
			Male:80-306
SGOT	**13**	IU/L	Female:2-31
			Male:2-37
SGPT	**17**	IU/L	2-38
Gamma Glutamyltranfrase	**26**	IU/L	Female:0-32
			Male:0-49
CRP(h-S).	**0.1**	mg/L	0-10

Urine Biochemistry

Prophobilinogen	**Negative**
Coproporphirin	**Positive**
Uroporphyrin	**Trace**

سیستم تمام اتوماتیک فول کاپیلاری Sebia cap 2(Felex
سیستم الکتروفورز اتوماتیک HYDRASYS 2
آزمایش سرب به صورت روزانه انجام میشود.

Immunology & Serology

Test	Result	Unit	Method	Normal Value
Immunology & Immunopathology				
C3	**1.185**	G/L		0.89-1.87
C4 (Turbidometry)	**0.336**	G/L		0.165-0.380
C1 Inhibitor	**0.42**			Less than 0.24 C1 inhibotor defeciency
TTG-G chorus	**3**	IU/ml		>18 Positive
				<12 Negative
				12-18 Doubtful
TTG-A Chorus	**<3**	AU/ml		>18 Positive
				<12 Negative
				12-18 Doubtful
Immuno Assay of Infectious Disease				
Helico (IgG) Chorus	**9.2**	AU/ml		>12 Positive

Infectious Disease & Immunodignostics

Checked By F.Ra

Test	Risk	Result	Unit	Reference(Based on Sex/Age)
Fecal Calprotectin ;F.C-ELISA	H	66.29	Ug/dL	Normal : Up to 50 Mild organic disease : 50-200 Indicate of active disease with inflammation in the GI : > 200

HPLC Department

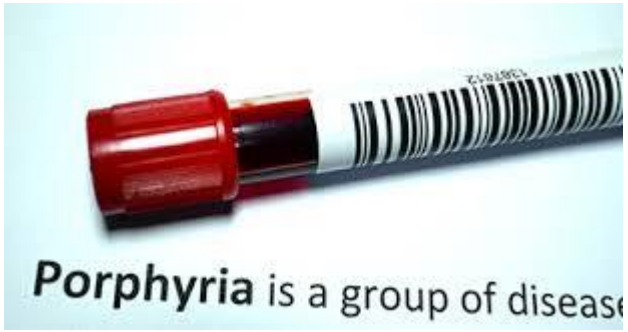
Checked By A.Rostam

Test	Risk	Result	Unit	Reference(Based on Sex/Age)
Porphyrin;Blood		Negative		Negative
Porphyrin;Stool		Positive		Negative

With the best regards .. Dr.M.r.Azizi , Dr.M.Vahid , Dr.M.Reisi Far

آزمایشگاه آرتوش
دکتر محمدرضا عزیزی
نظام پزشکی: ع.ت. ۱۰۵۰
دکتر محمد وحید
نظام پزشکی: ع.ت. ۱۰۸۷
دکتر ملک رئیسی فر
نظام پزشکی: ۲۰۸۳۳

- Urine ALA -
- Urine PBG -
- Coproporphyrin +
- Uroporphyrin trace
- Serum porphyrin -
- Fecal porphyrin +



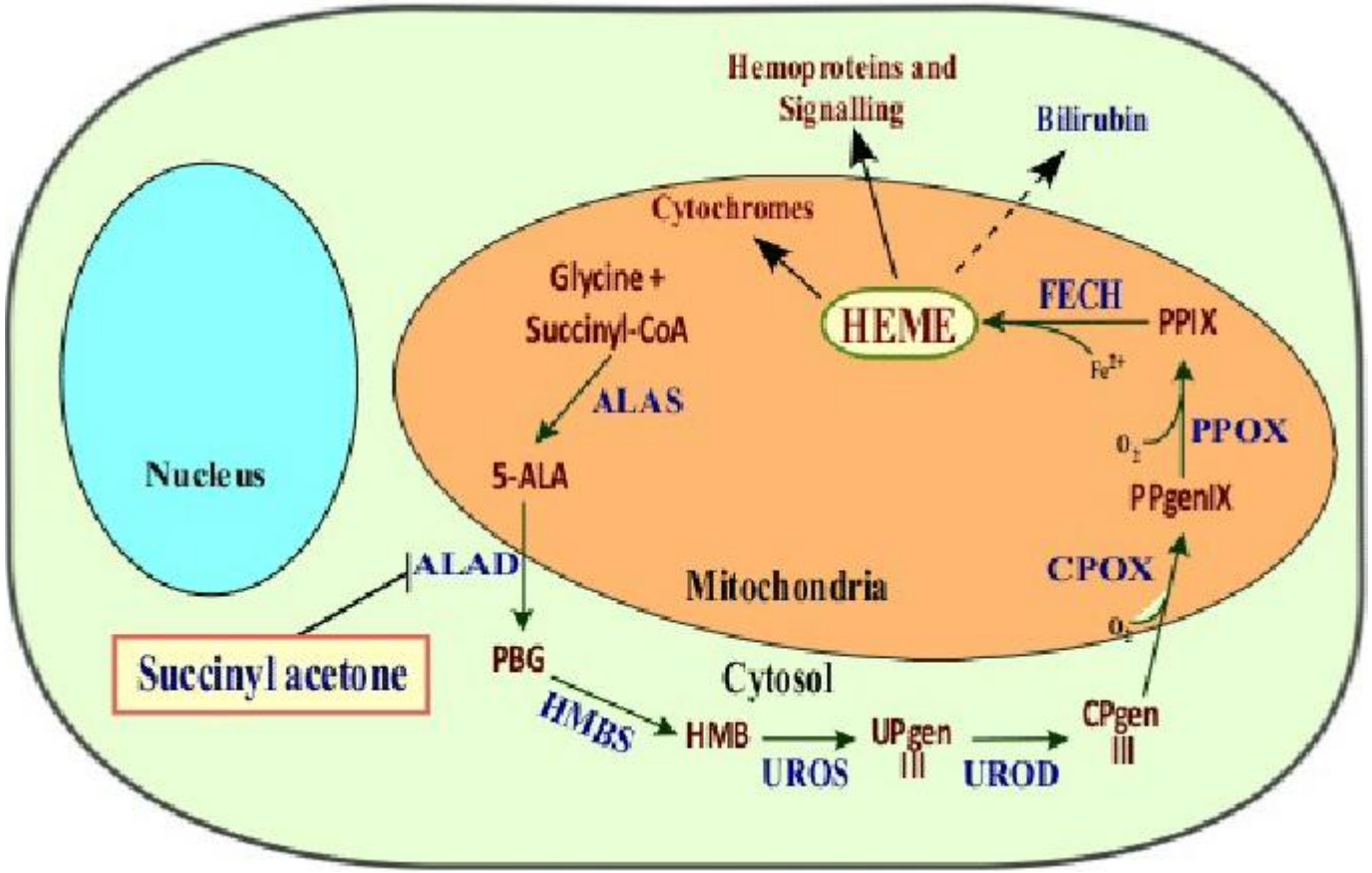
- HEREDITARY COPROPORPHYRIA (HCP)

Porphyrias

- Altered activities of enzymes of heme biosynthetic pathway.
- These enzymes most active in:

I. Bone marrow (~85% of daily heme synthesis)

II. Liver



8 enzymes active in all tissues.

Heme is required for hemoproteins:

- Hgb
- Myoglobin
- Respiratory cytochromes
- Cytochrome P450 enzymes (CYPs)

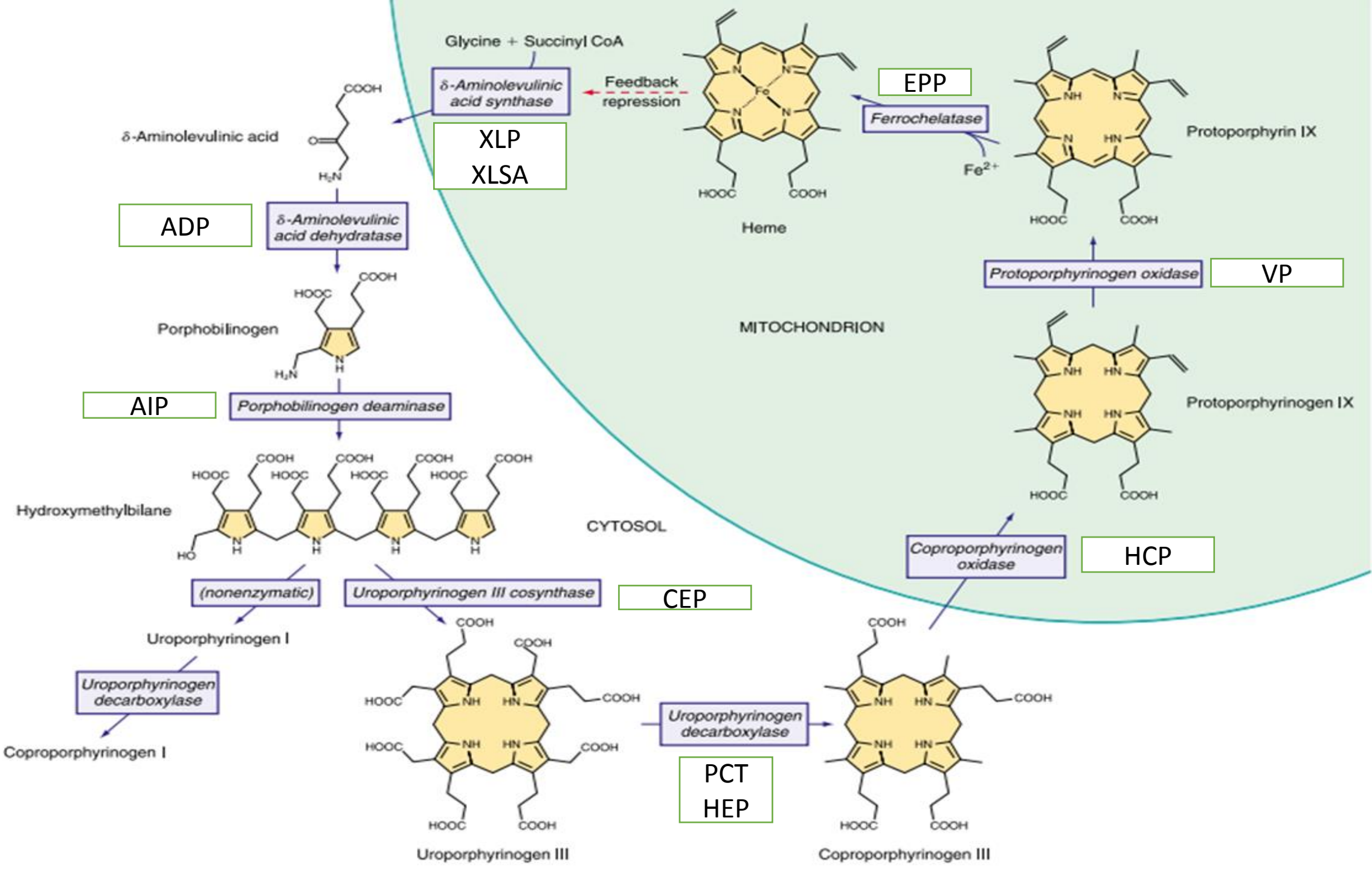


Table 112.1 The Human Porphyrias: Pathogenic Variants, Time of Presentation, and Tissue- and Symptom-Based Classifications

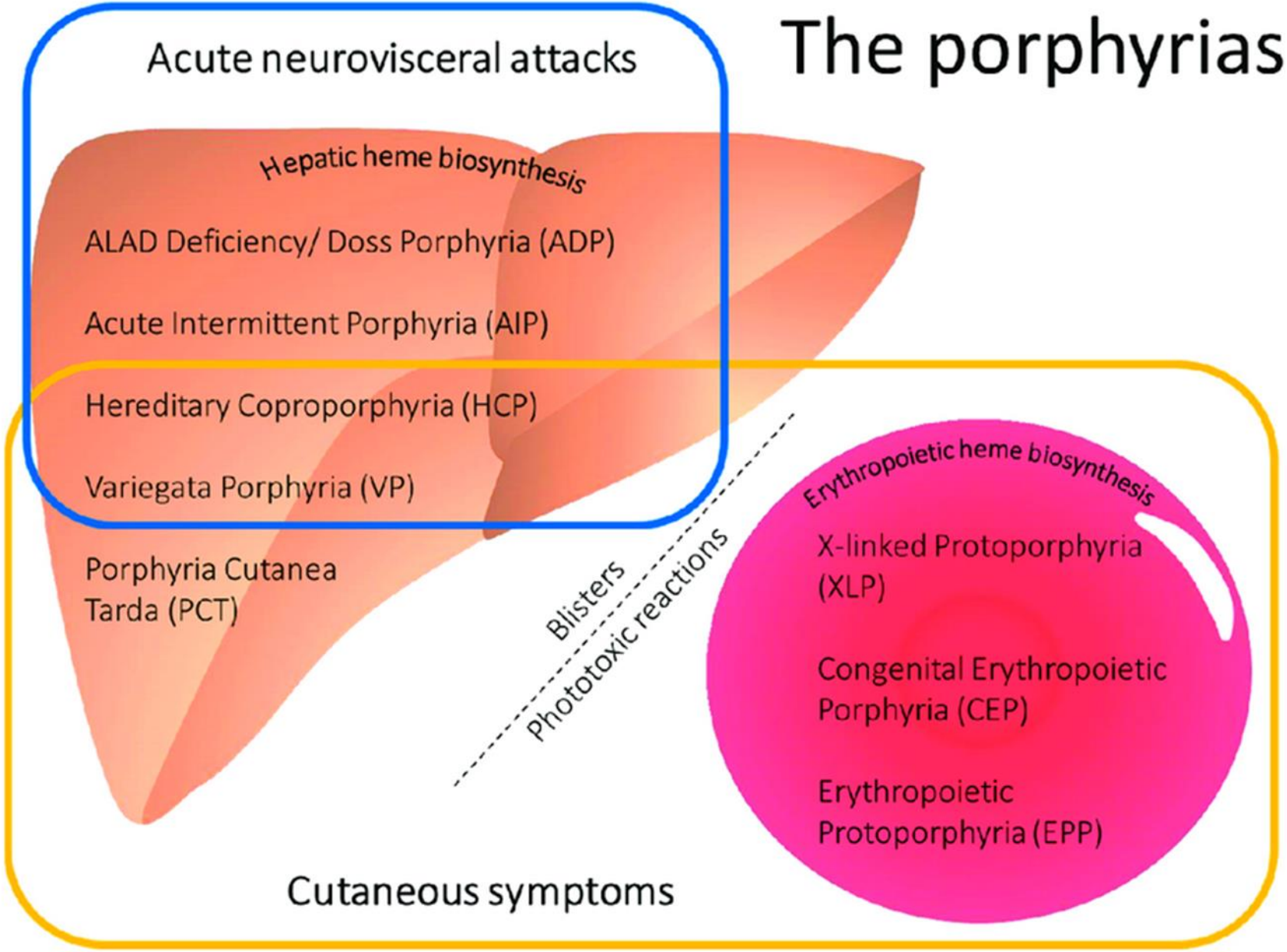
DISEASE	ENZYME	INHERITANCE	PRESENTATION	CLASSIFICATION*			
				H	E	A/N	C
X-linked protoporphyria (XLP)	δ-Aminolevulinate synthase 2 (ALAS2)	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	δ-Aminolevulinic acid dehydratase (ALAD)	Autosomal recessive	Mostly postpuberty	X	X‡	X	
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase (HMBS)	Autosomal dominant	Postpuberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase (UROS)	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	Uroporphyrinogen decarboxylase (UROD)	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X‡		X
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase (CPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	Ferrochelatase (FECH)	Autosomal recessive (most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*Classification abbreviations: H, Hepatic; E, Erythropoietic; A/N, Acute/Neurologic; C, Cutaneous.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT. Other genetic factors, such as HFE pathogenic variants, are sometimes found in all types of PCT.
‡ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.

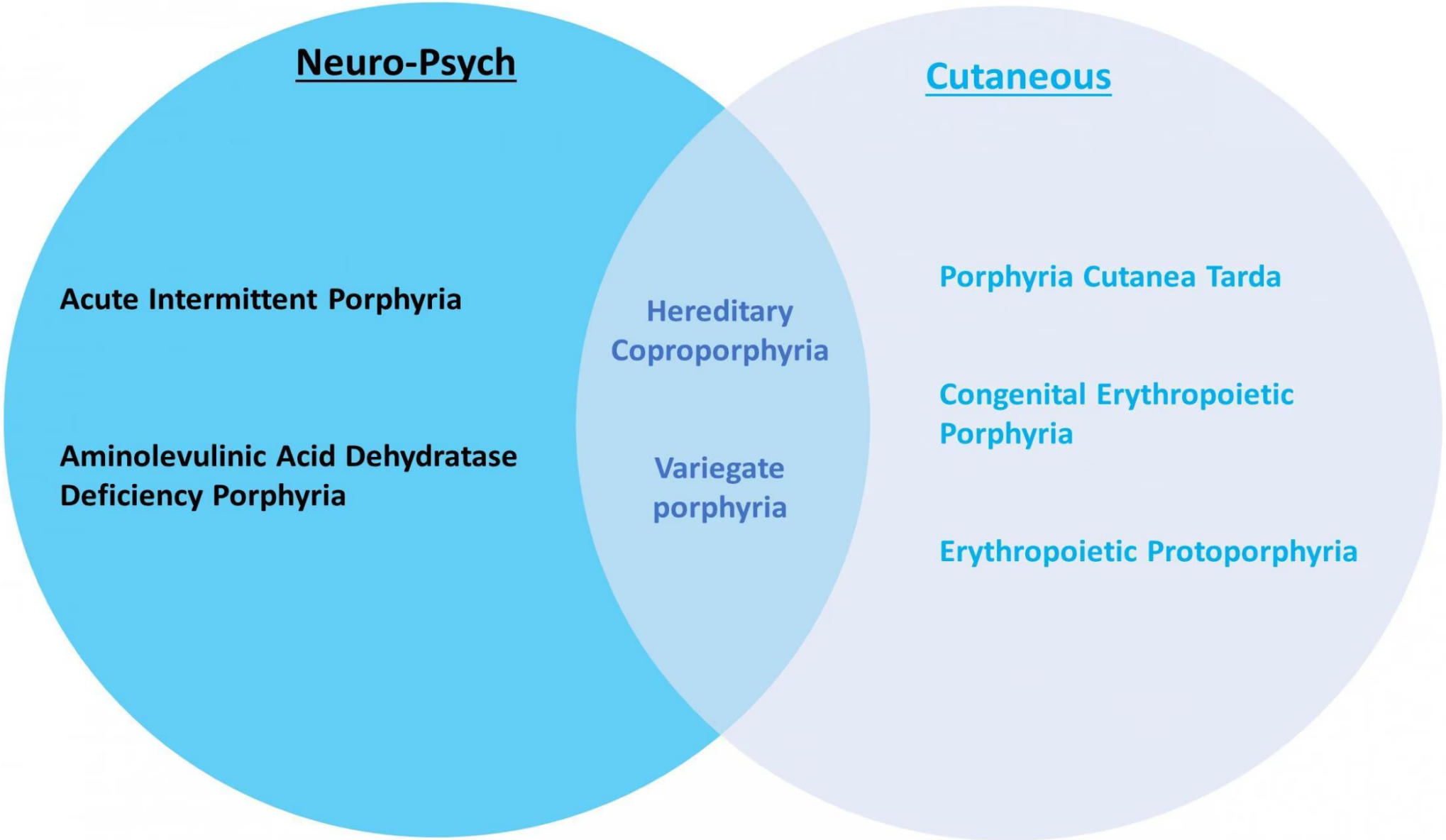
The porphyrias

- ❖Hepatic
- ❖Erythropoietic

- ❑Acute nourologic
- ❑Cutaneous:
  - Blistering
  - Nonblistering



CLASSIFICATION AND DIAGNOSIS OF PORPHYRIAS



Classification of Porphyrias

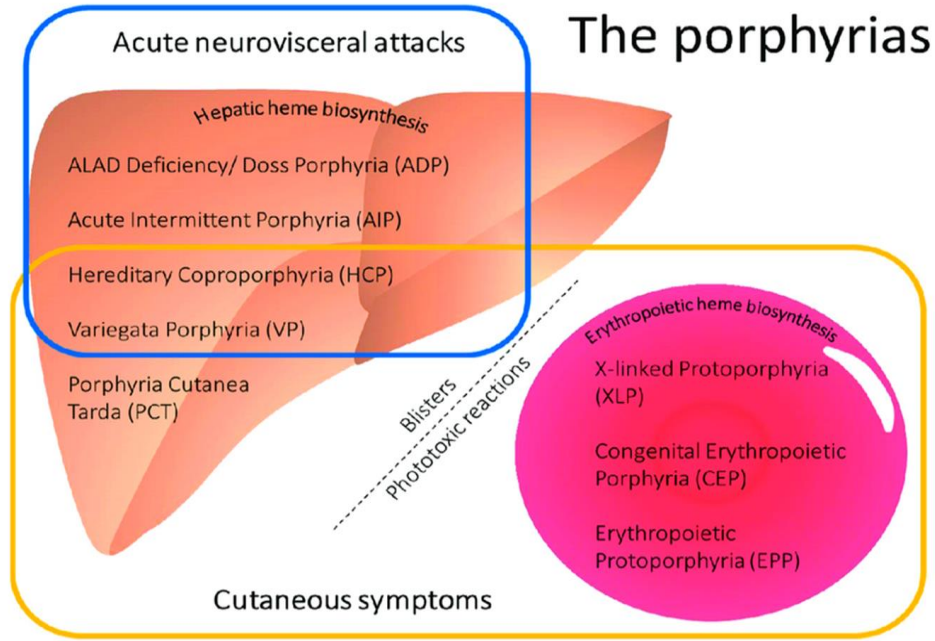
a. Acute (neurovisceral) without any cutaneous lesions
   - Acute intermittent porphyria (AIP)
   - ALA dehydratase deficiency porphyria (ALADP)

b. Acute (neurovisceral) with blistering cutaneous lesions
   - Variegate porphyria (VP)
   - Hereditary coproporphyria (HCP)

c. Non-acute (non-neurovisceral) with blistering cutaneous lesions
   - Porphyria cutanea tarda (PCT)
   - Hepatic erythropoietic porphyria (HEP)
   - Congenital erythropoietic porphyria (CEP)

d. Acute photosensitivity and non-blistering lesions
   - Erythropoietic porphyria (EPP)

e. Acquired
   - Porphyria cutanea tarda (PCT)

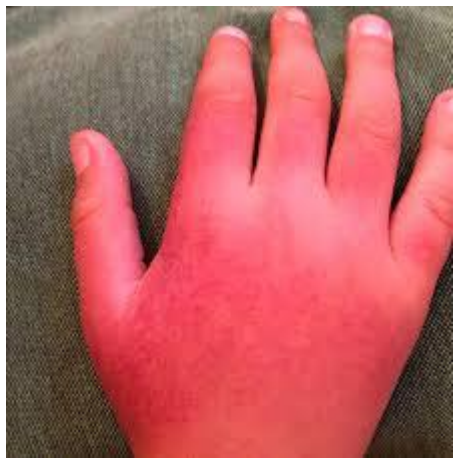


Acute porphyrias characterized by possible onset of recurrent acute attacks of non-specific but very severe and potentially life-threatening neurovisceral symptoms (acute porphyric attacks)
They are rare and mostly inherited diseases.

Table 112.4 Common Presenting Symptoms and Signs of Acute Porphyria

SYMPTOMS AND SIGNS	FREQUENCY (%)	COMMENT
GASTROINTESTINAL		
Abdominal pain	85–95	Usually unremitting (for hours or longer) and poorly localized but can be cramping.
Vomiting	43–88	Neurologic in origin and rarely accompanied by peritoneal signs, fever, or leukocytosis.
Constipation	48–84	Nausea and vomiting often accompany abdominal pain. May be accompanied by bladder paresis.
Diarrhea	5–12	
NEUROLOGIC		
Pain in extremities, back	50–70	Pain may begin in the chest or back and move to the abdomen. Extremity pain from the chest, neck, or head indicates involvement of sensory nerves; objective sensory loss reported in 10–40% of cases.
Paresis	42–68	May occur early or late during a severe attack. Muscle weakness usually begins proximally rather than distally and more often in the upper than lower extremities.
Respiratory paralysis	9–20	Preceded by progressive peripheral motor neuropathy and paresis.
Mental symptoms	40–58	May range from minor behavioral changes to agitation, confusion, hallucinations, and depression.
Convulsions	10–20	A central neurologic manifestation of porphyria or caused by hyponatremia, which often results from syndrome of inappropriate antidiuretic hormone secretion or sodium depletion.
CARDIOVASCULAR		
Tachycardia	64–85	May warrant treatment to control rate, if symptomatic.
Systemic arterial hypertension	36–55	May require treatment during acute attacks, and sometimes becomes chronic.

From Anderson KE, Bloomer JR, Bonkovsky HL, et al. Desnick recommendations for the diagnosis and treatment of the acute porphyrias, *Ann Intern Med.* 2005;142(6):439–450.



Skin symptoms restricted to sun exposed area

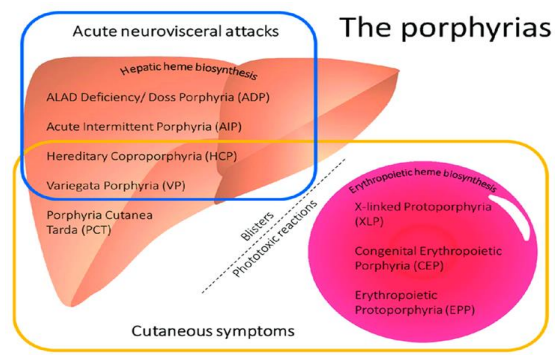
↓

Suspect cutaneous porphyria: EPP, HCP, PCT, VP, XLPP

↓

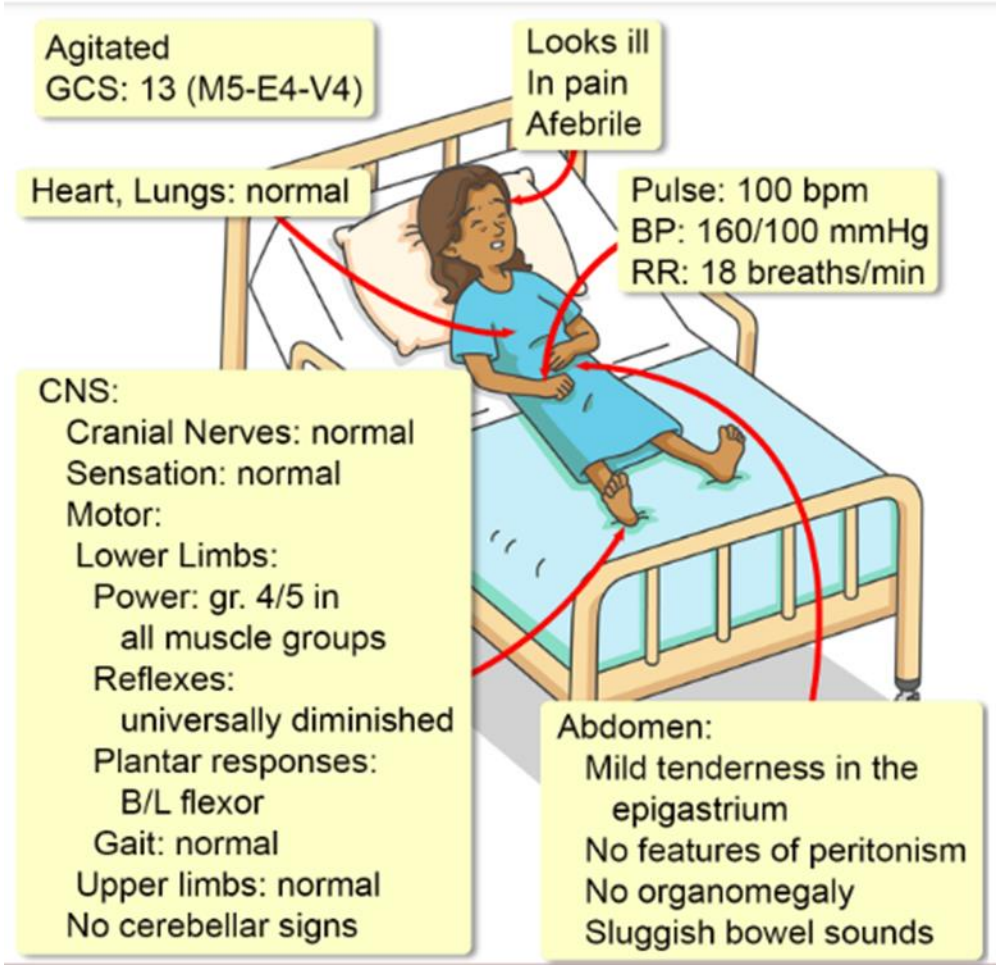
Symptoms

• Edema • Painful photodermatitis • Urticaria	• Blistering lesions • Skin fragility • Scarring • Hypertrichosis
↓	↓
Suspect EPP/XLPP	Suspect PCT/HCP/VP
↓	↓
Check plasma fluorescence and erythrocyte free and zinc protoporphyrin to diagnose either EPP or XLPP.	Check plasma fluorescence and urinary and fecal porphyrin profile. Diagnose the type of porphyria according to its characteristic profile.

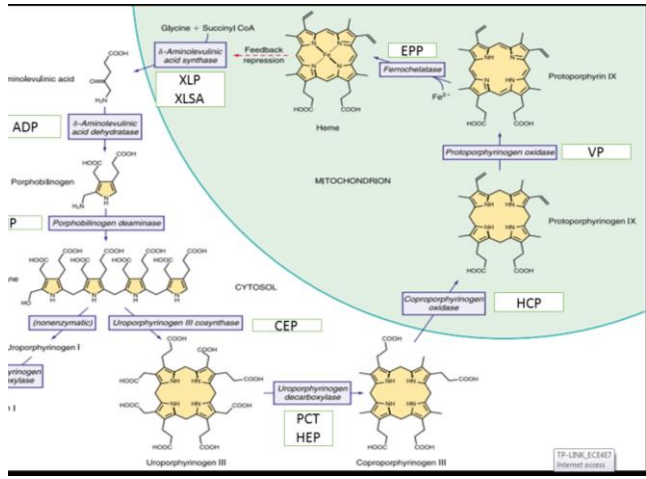


Most porphyrias are hepatic

- Activation of hepatic porphyrias is very rare during childhood
- Hepatic regulatory of heme biosynthese influence by pubertal development
- Homozygous forms of hepatic porphyrias may manifest before puberty
- Children heterozygous for hepatic porphyrias may present with nonspecific and unrelated symptoms

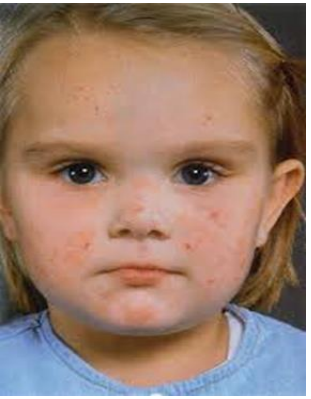


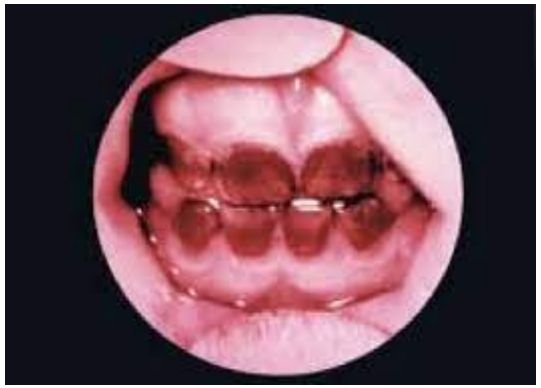
↑heme pathway intermediates primarily in bone marrow erythroid cells



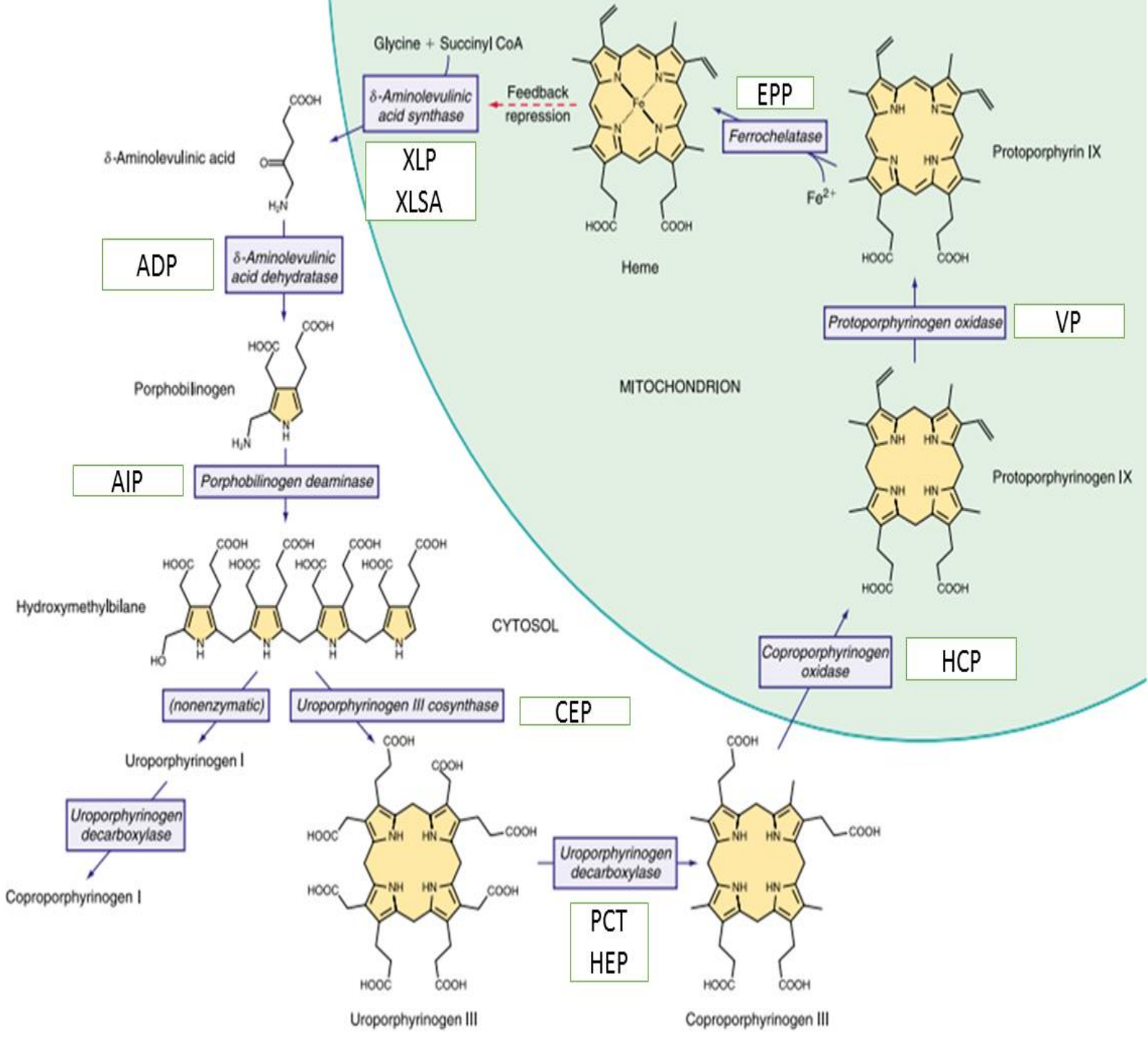
- Erythropoietic porphyrias, Usually present at birth or in early childhood with cutaneous photosensitivity

- Congenital erythropoietic porphyria, even in utero as nonimmune hydrops.
- Erythropoietic protoporphyria is most common porphyria in children.





- ALA and PBG are excreted in urine.
- Excretion of porphyrins in urine or bile is determined by number of carboxyl groups.
- Many carboxyl groups, such as uroporphyrin(octacarboxyl 8 porphyrin) and heptacarboxyl 7 porphyrin, are water soluble and readily excreted in urine.
- Fewer carboxyl groups, such as protoporphyrin (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces.
- Coproporphyrin (tetracarboxylporphyrin) is excreted partly in urine and partly in bile.



Panel of porphyria

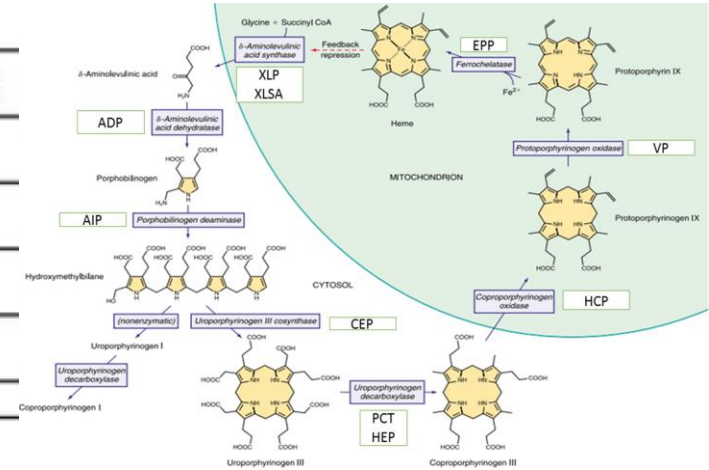
➢URINE

- ALA
- PBG
- Uroporphyrin
- Heptacarboxyl porphyrin
- Hexacarboxyl porphyrin
- Pentacarboxyl porphyrin
- Coproporphyrin 1
- Coproporphyrin 3

➢RBC

- Protoporphyrine

Hepatic Porphyrias (normal RBC Porphyrins)	Erythropoietic Porphyrias (↑ RBC Porphyrins)
Acute Intermittent Porphyria (**AIP**)	Congenital Erythropoietic Porphyria (**CEP**)
Variegate porphyria (**VP**)	Erythropoietic Protoporphyria (**EP**)
Hereditary Coproporphyria (**HCP**)	
Porphyria Cutanea Tarda (**PCT**)	

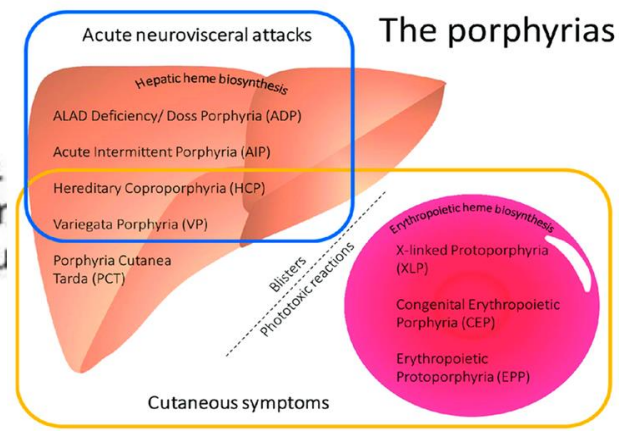


Presentation:	Porphyrias	Tests to order	Sample
Acute symptoms	AIP	1. Urine Porphyrin Precursors Screen & Quantitation	Random (50 ml) or 24-h with Tartaric acid
Acute symptoms + skin lesions (may occur independently)	VP HCP	2. Feces Porphyrins Screen & Quantitation	Random
Skin lesions	PCT CEP EP	1. Urine Porphyrin Precursors Screen & Quantitation 2. Feces Porphyrins Screen & Quantitation 3. Urine Porphyrins Screen & Quantitation 4. RBC Porphyrins Screen & Quantitation	Random (50 ml) or 24-h with Tartaric acid Random Random (50 ml) or 24-h with Na_2CO3 Lavender-top (EDTA) blood; need Hct

Notes:

At time of acute attack:

1. Collect a random urine sample first (50 ml with no preservatives), before attempting to collect a 24-h sample.
2. Request "Porphyrin Precursors" (ALA & PBG) instead of "Porphyrins" screen and quantitation. The Laborator have to adjust pH to 4-6 for "Porphyrin Precursors", but pH 8-10 for "Porphyrins". - The commonest problem cau confusion!
3. All sample containers should be covered with tin foil to shield off from light.

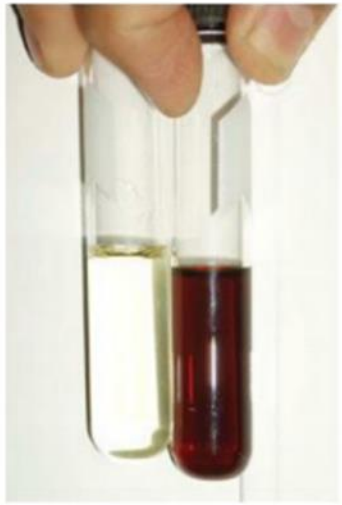


- Whereas porphyrin precursors ALA and PBG are colorless, nonfluorescent, and excreted unchanged in urine, PBG may degrade to colored products such as brownish pigment called porphobilin or spontaneously polymerize to uroporphyrins.

- Porphyrins are red in color and display bright-red fluorescence when exposed to long-wave length ultraviolet (UV) light.

Urine may appear purple during an attack or after standing in light

The amount of porphobilinogen (PBG) in urine is increased during attacks of AIP.



- There are three acute porphyrias that can cause increases in PBG, namely AIP, Hereditary Coproporphyria (HCP) and Variegate Porphyria (VP). Acute attacks can occur in all of these conditions. Skin photosensitivity can occur in HCP and VP, but not AIP.

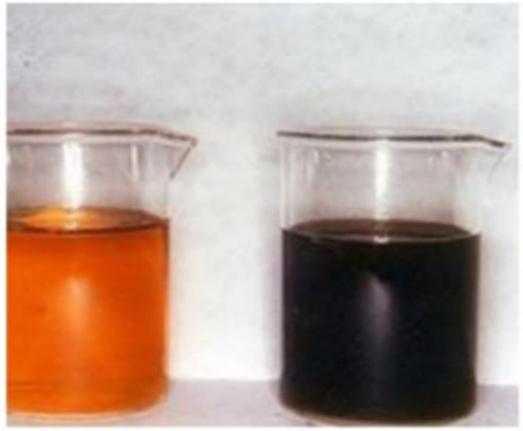


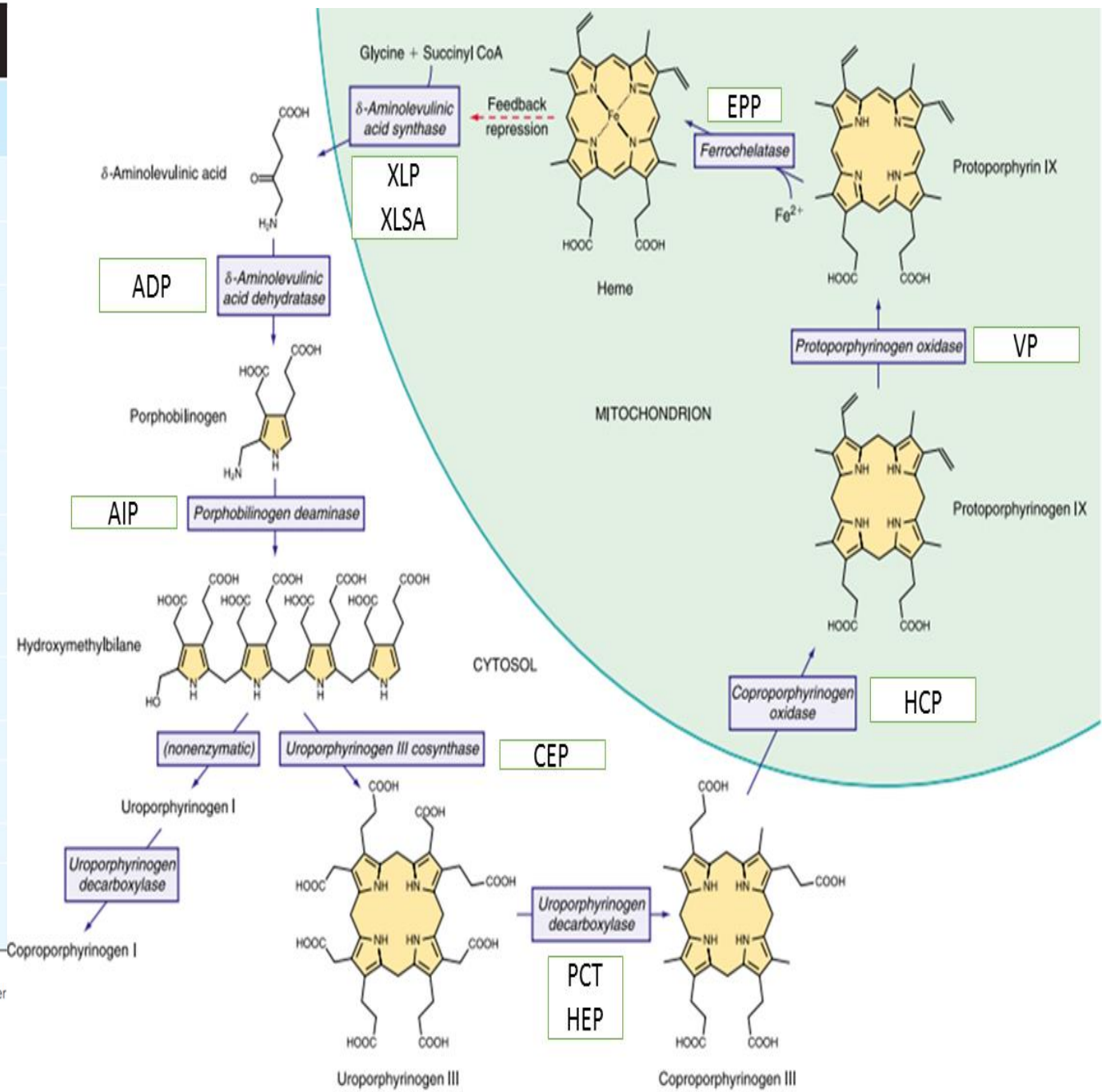
Table 112.1 The Human Porphyrias: Pathogenic Variants, Time of Presentation, and Tissue- and Symptom-Based Classifications

DISEASE	ENZYME	INHERITANCE	PRESENTATION	CLASSIFICATION* H	E	A/N	C
X-linked protoporphyria (XLP)	δ-Aminolevulinate synthase 2 (ALAS2)	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	δ-Aminolevulinic acid dehydratase (ALAD)	Autosomal recessive	Mostly postpuberty	X	X‡	X	
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase (HMBS)	Autosomal dominant	Postpuberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase (UROS)	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	Uroporphyrinogen decarboxylase (UROD)	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X‡		X
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase (CPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	Ferrochelatase (FECH)	Autosomal recessive (most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*Classification abbreviations: H, Hepatic; E, Erythropoietic; A/N, Acute/Neurologic; C, Cutaneous.

†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT. Other genetic factors, such as HFE pathogenic variants, are sometimes found in all types of PCT.

‡ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.



considering all age-groups, and are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy .

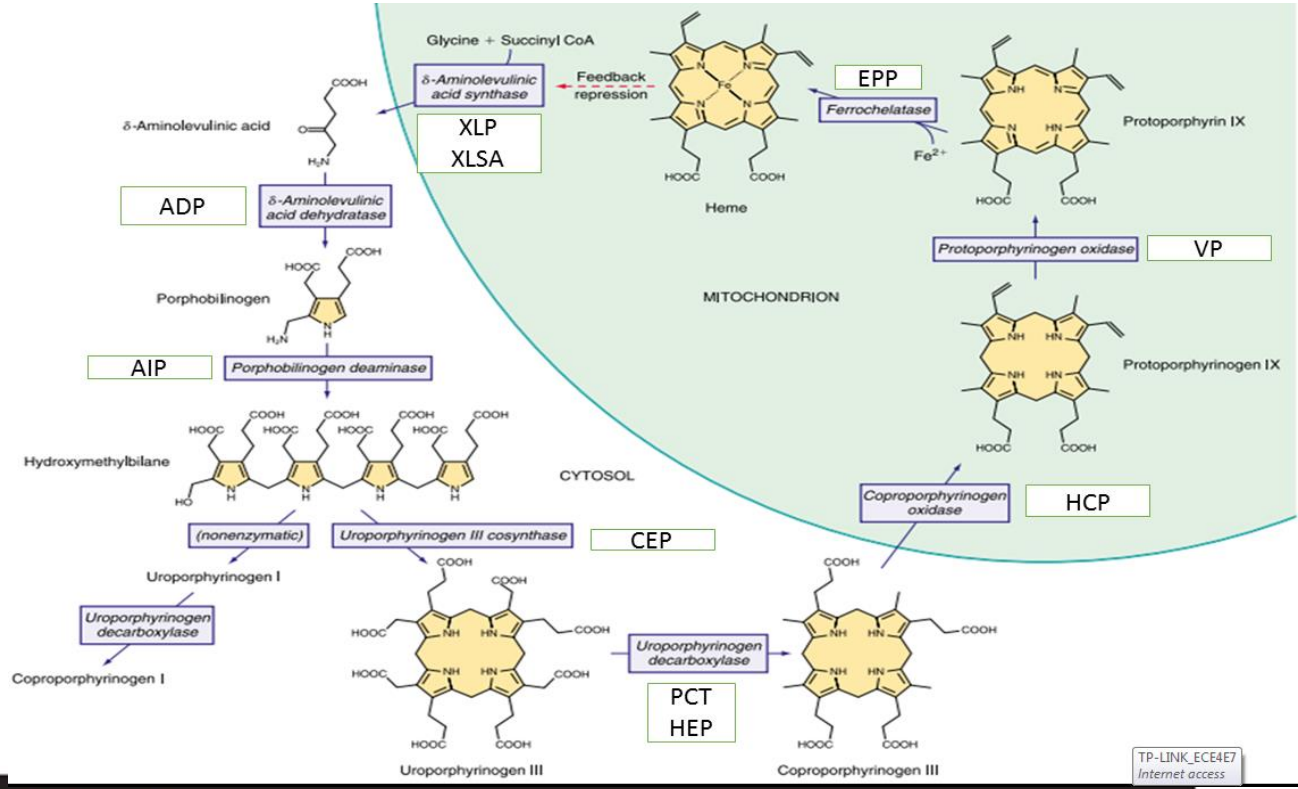


Table 112.2 The Three Most Common Human Porphyrias and Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450 inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose, givosiran
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma or urine porphyrins	Phlebotomy, low-dose hydroxychloroquine, direct acting antivirals (if hepatitis C is present)
Erythropoietic protoporphyria	Phototoxic pain and swelling (mostly acute), childhood onset	Sunlight exposure	Total erythrocyte protoporphyrin with metal-free and zinc protoporphyrin	Sun protection

- Givosiran Sodium is a small interfering RNA (siRNA) therapeutic that targets aminolevulinic acid synthase 1 (ALAS1), rate-limiting enzyme

- By downregulating expression of ALAS1, reduces production of ALA and PBG, thereby alleviating symptoms

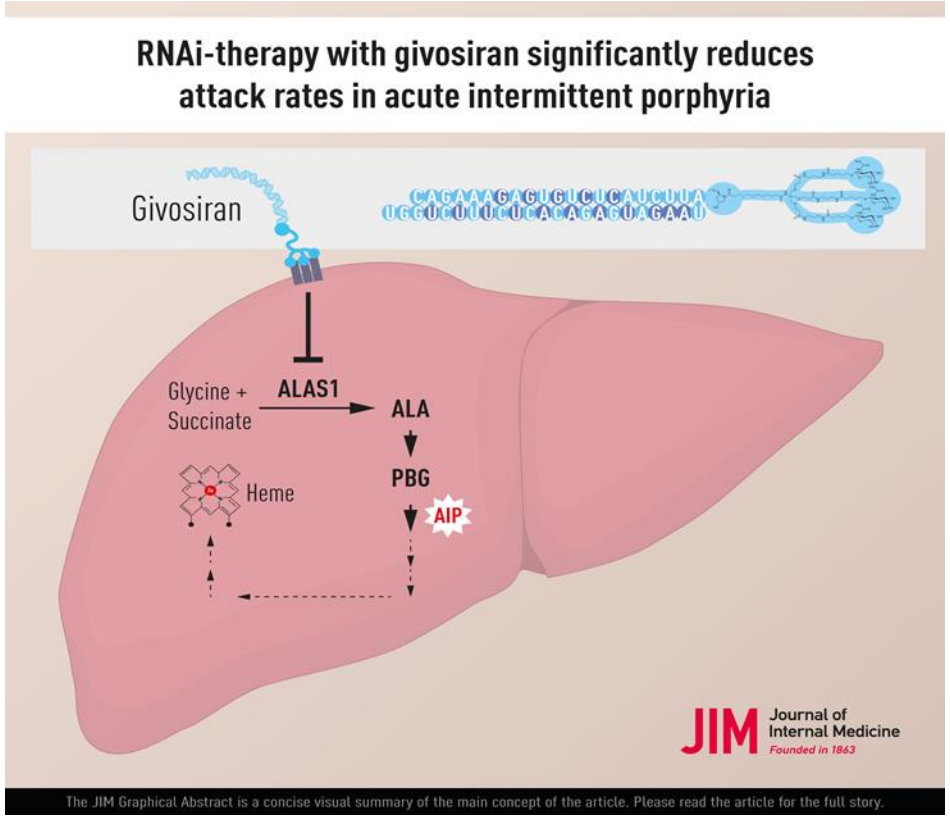


Table 112.3 Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates (all)	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen (paracetamol)
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam‡	Ranitidine†
Primidone*	Acetazolamide
Valproic acid*	Allopurinol
Pyrazolones (aminopyrine, antipyrine)	Amiloride
Griseofulvin*	Bethanidine
Ergots	Bumetanide
Metoclopramide* ‡	Coumarins
Rifampin*	Fluoxetine
Pyrazinamide* ‡	Gabapentin
Diclofenac* ‡	Gentamicin
Fluconazole*	Guanethidine
Oral contraceptives	Ofloxacin
Progesterone and synthetic progestins*	Propranolol
Danazol*	Succinylcholine
Alcohol	Tetracycline
ACEIs (especially enalapril) ‡	
Spironolactone	
CCBs (especially nifedipine) ‡	
Ketoconazole	
Ketamine*	

*Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria but have been implicated as harmful in acute porphyrias, mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate porphyria cutanea tarda, there is little evidence they are harmful in the acute porphyrias.

†Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.

‡These drugs have been classified as probably safe by some sources, but this is controversial, and they should be avoided.

This partial listing does not include all available information about drug safety in acute porphyrias. Other sources should be consulted for drugs not listed here.

ACEIs, Angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

Table 4 Adult reference ranges

Specimen	*Analyte*	*Reference range*
Urine	Porphobilinogen	<10 μmol/l <1.5 μmol/mmol creatinine
	Total porphyrin	20–320 nmol/l <35 nmol/mmol creatinine
Faeces	Total porphyrin	10–200 nmol/g dry wt
Erythrocytes	Total porphyrin	0.4–1.7 μmol/l

Urinary porphyrin: creatinine ratios are higher in children weighing less than 30 kg or less than 9 years old.[10]
The reference range for erythrocytes refers to packed erythrocytes.

Environmental factors

- Environmental factors with key role in triggering disease:

➢Drugs

➢Calorie restriction

➢Hormones

➢Infections

➢Alcohol abuse

- Some aspects involved in pathogenesis of diseases remain ill-defined and diagnosis still represents diagnostic challenge for clinicians.

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Multiform clinical manifestations

- Acute porphyrias are often misdiagnosed diseases due to multiform clinical manifestations, which can mimic many other (and more common) diseases

- Many different specialists involve in diagnosing and managing :

➢Surgeons

➢Psychiatrists

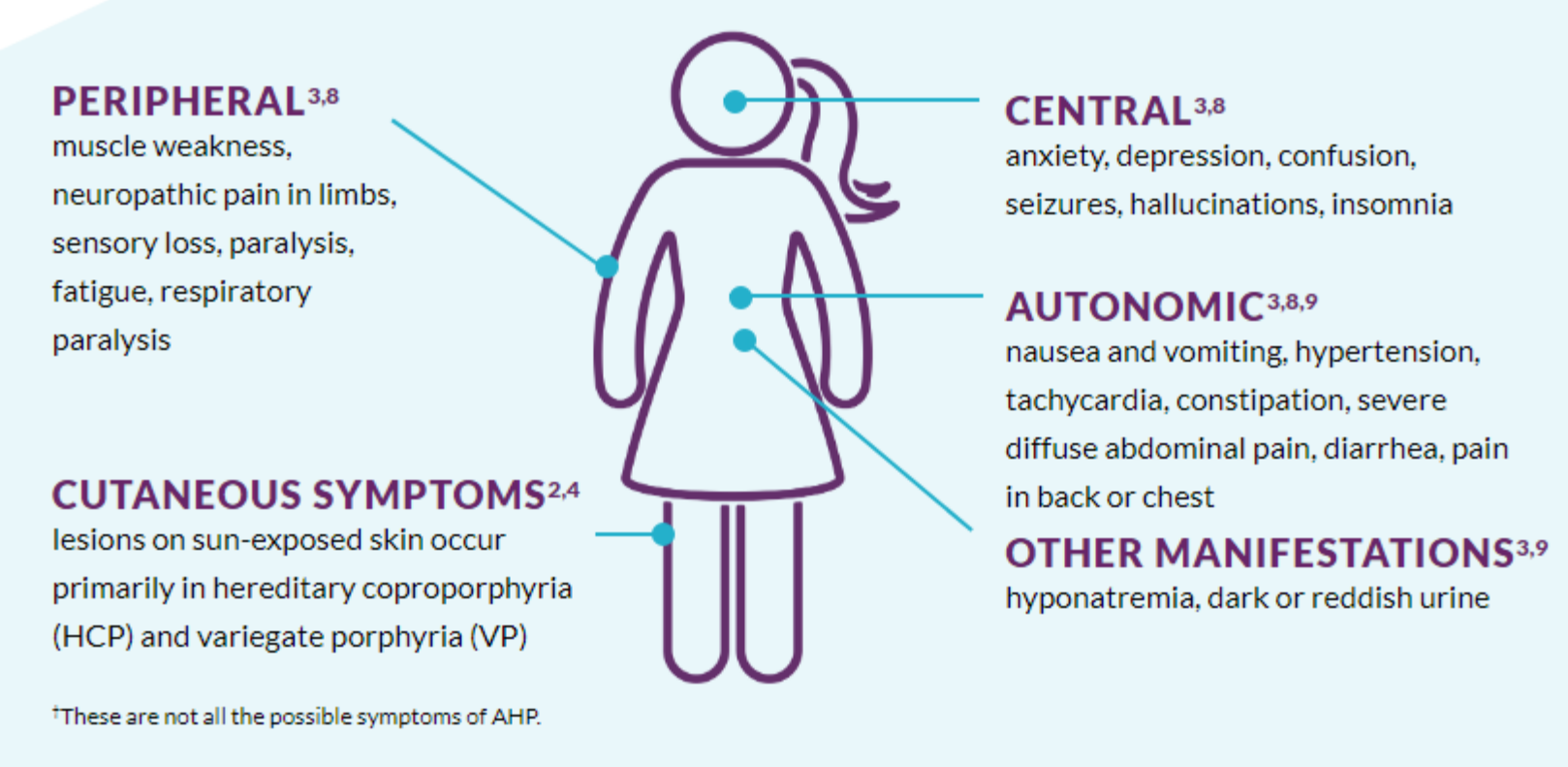
➢Gastroenterologists

➢Neurologists

➢Emergency physicians

. Step 1 — diagnosis of acute porphyric attack

- Clinical features



cardinal sign of an acute porphyria

- Most common complaint is a severe abdominal pain, mimicking an “acute abdomen”
- Nausea and vomiting
- Neurological and psychiatric symptoms [depression and apathy to extreme agitation or psychosis with hallucinations]
- Back pain extending to proximal limbs
- Signs of vegetative dysfunction (HTN with postural hypotension, tachycardia and constipation)
- An acute attack may preceded by behavioural changes such as anxiety, irritability, restlessness and insomnia, and may rapidly into symptoms of severe autonomic and acute motor and sensory neuropathy.
- Muscular weakness, in particular proximal motor neuropathy (resembling Guillain–Barre syndrome), is quite common. It can progress to general paralysis, leading to severe respiratory impairment up to death from cardiorespiratory arrest.
- Hyponatremia and hypomagnesemia may occur as a result of dehydration nephrotoxicity or SIADH
- These water/electrolyte disorders may contribute to neurological and psychiatric symptoms of acute porphyric attack
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Table 3
Differential diagnosis of acute porphyric attack — common clinical conditions mimicked by an acute porphyric attack.

Surgical Conditions Associated with acute abdomen
(Peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, etc.)
Dismetabolic/Disendocrine conditions
Acute hypoadrenalism (Addisonian crisis)
Acute hypoparathyroidism and hypocalcemic crisis
Pheocromocytoma
Neurolopsychiatric conditions
Guillain–Barre' syndrome
Emicrania
Acute psychotic attack
Delirium
Acute panic attack
Epilepsy
Acute myopathies
Cardiovascular conditions
Hypertensive crisis
Tachyarrhythmia
Haematological conditions
Acute haemolytic crisis
Acute drepanocytic crisis
Gastroenterological conditions
Acute gastroenteritis with vomiting

- Symptoms of cutaneous photosensitivity begin in childhood and consist of acute pain and itching, often occurring within minutes of sunlight exposure and followed by redness and swelling with continued exposure

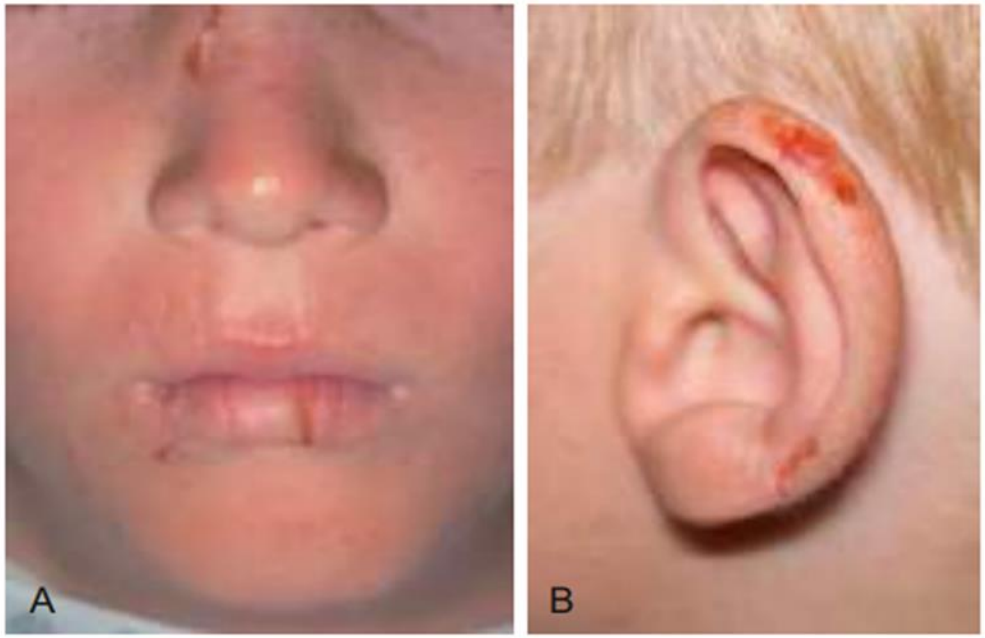


Fig. 112.7 Erythropoietic protoporphyria (EPP). **A,** Linear erosions of the lateral nasal bridge and lower lip in a patient with EPP. **B,** Erosions with crusting on the left helix of a patient with EPP. (*From Horner ME, Alikhan A, Tintle S, et al. Cutaneous porphyrias. Part 1. epidemiology, pathogenesis, presentation, diagnosis, and histopathology. Int J Dermatol. 2013;52:1464–1480, Figs. 7 and 8.*)

Erythrodontia

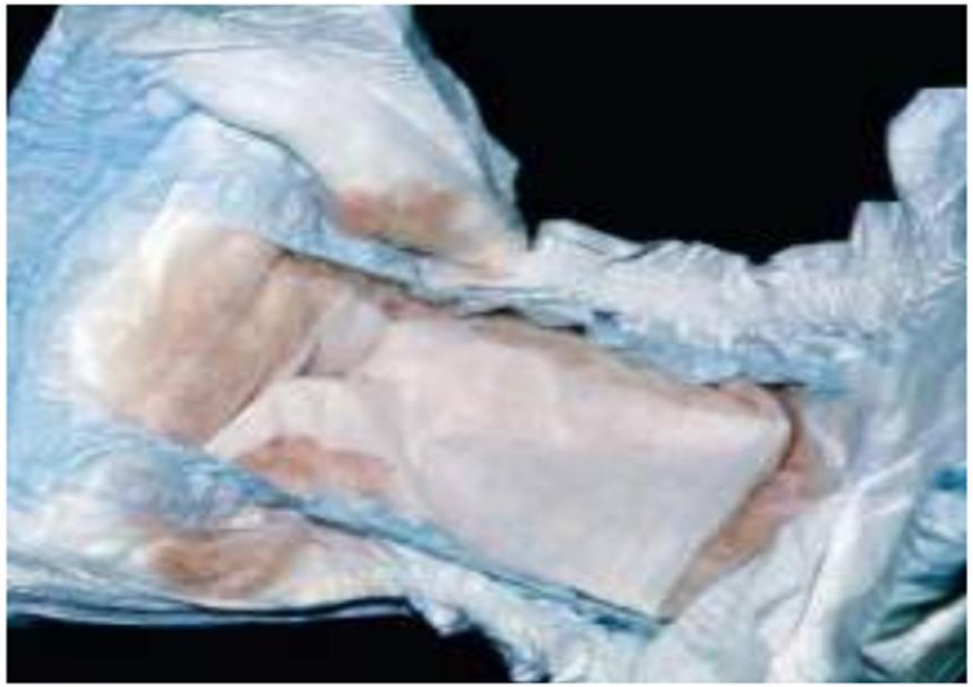


Fig. 112.2 Congenital erythropoietic porphyria (CEP). The diaper of a baby with CEP demonstrates the red color of urine. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)

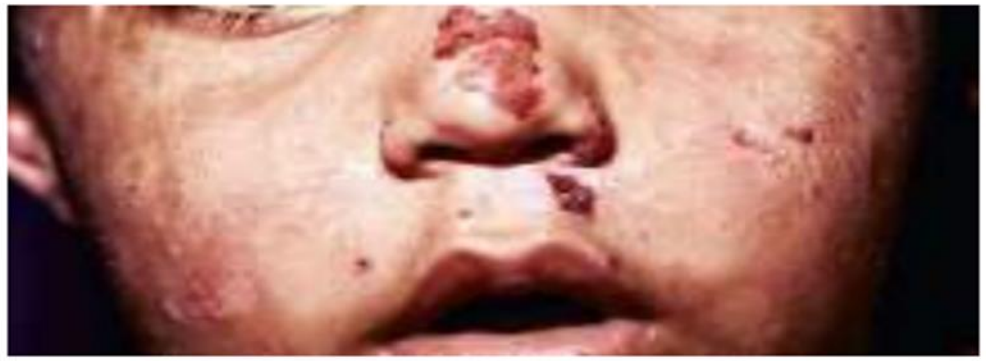


Fig. 112.3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)

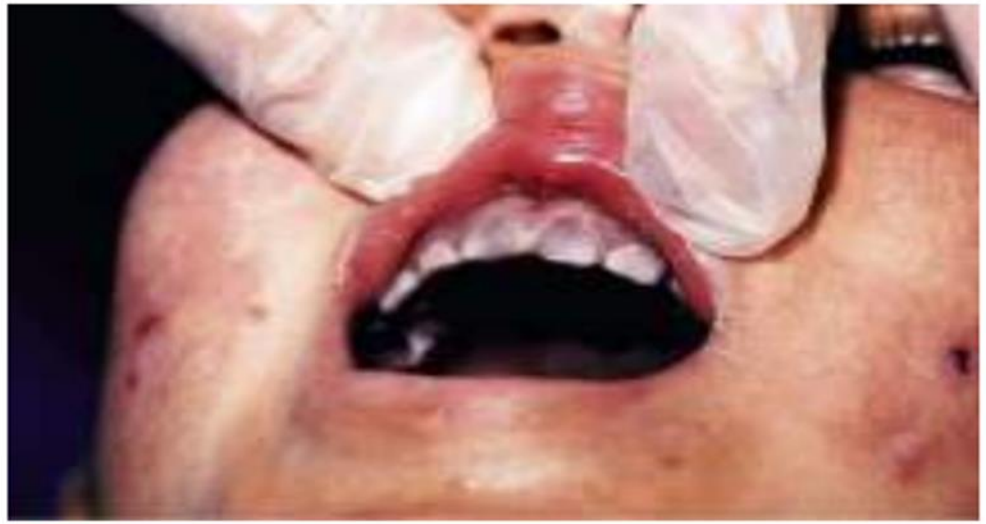


Fig. 112.4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood's lamp examination. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)

PCT

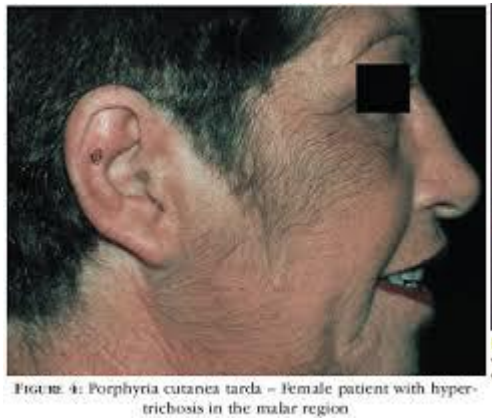


Figure 4: Porphyria cutanea tarda – Female patient with hypertrichosis in the malar region

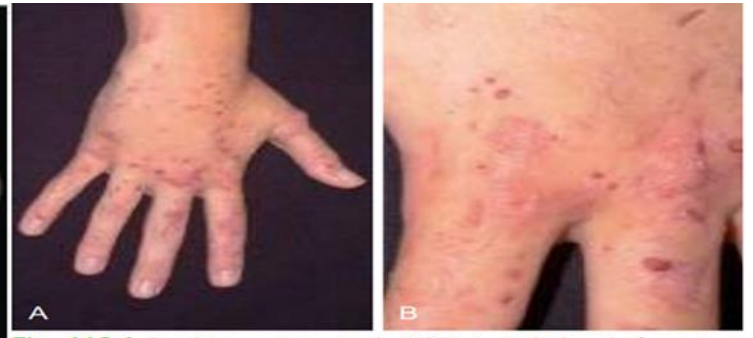


Fig. 112.6 Porphyria cutanea tarda (PCT). A, Right hand of a patient with PCT, revealing numerous erosions and erythematous patches. B, Close-up of right hand. (*From Horner ME, Alikhan A, Tintle S, et al. Cuta-*

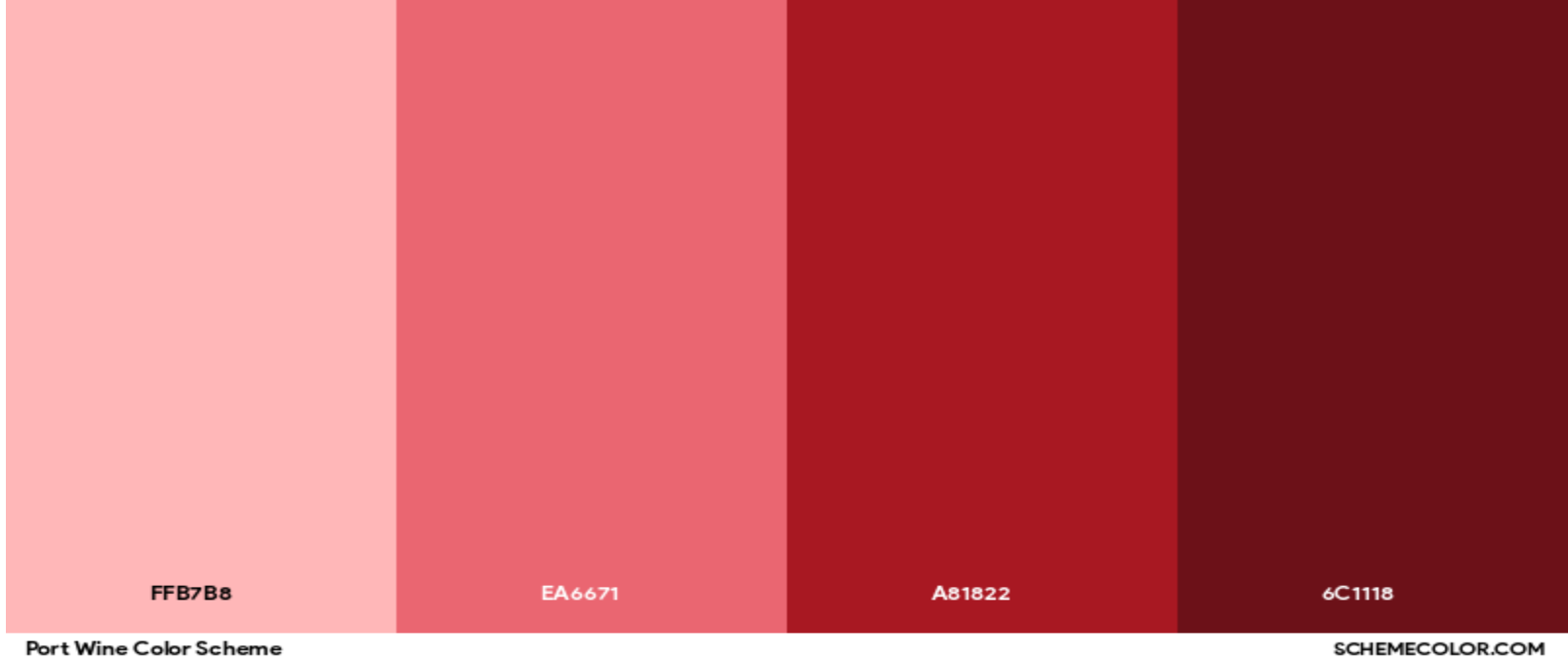
- Blistering and crusted skin lesions on backs of hands, sun-exposed areas of body, and less often on forearms, face, ears, neck, legs, and feet.
- Heal slowly, and are subject to infection.
- Skin is friable, and minor trauma may cause blisters or denudation of skin
- Facial hypertrichosis and hyperpigmentation are also common.
- Severe scarring and thickening of sun-exposed skin may resemble scleroderma.

Diagnosis of acute porphyria should be considered in any patient presenting with symptoms that are prevalent in these conditions:

- Abdominal pain, if evaluation is not suggestive of other causes
- A diagnostic suspicion may be provided by urine darkening on standing in sunlight (half an hour is enough)

Table 3
Differential diagnosis of acute porphyric attack — common clinical conditions mimicked by an acute porphyric attack.

Surgical Conditions Associated with acute abdomen
(Peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, etc.)
Dismetabolic/Disendocrine conditions
Acute hypoadrenalism (Addisonian crisis)
Acute hypoparathyroidism and hypocalcemic crisis
Pheocromocytoma
Neurolopsychiatric conditions
Guillain–Barre' syndrome
Emicrania
Acute psychotic attack
Delirium
Acute panic attack
Epilepsy
Acute myopathies
Cardiovascular conditions
Hypertensive crisis
Tachyarrhythmia
Haematological conditions
Acute haemolytic crisis
Acute drepanocytic crisis
Gastroenterological conditions
Acute gastroenteritis with vomiting



- A diagnostic suspicion by urine darkening (red tint varying from port wine to diluted strawberry sap) on standing in sunlight (half an hour)

- As an effect of spontaneous polymerization of urinary PBG to uroporphyrins and other pigments (enhanced by sun exposure)

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- Although even a single specific symptom should lead to consider diagnosis, in patient with abdominal pain :

✓Dark/reddish urine

✓New-onset hypertension

✓Hyponatremia

✓Proximal muscle weakness

✓Recent use of drugs known to exacerbate porphyria

✓Recent calorie restriction diets

✓Alcohol abuse

Age at clinical onset may also be relevant:

- ALA-D deficiency porphyria, start in early infancy
- CEP, EPP in early infancy

- AIP, HCP, and VP have never been reported before puberty

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- HCP and VP ,CEP , PCT →Blistering cutaneous porphyria
- Skin fragility and bullous eruptions may be relevant presenting symptoms

- EPP, XLP → Nonblistering cutaneous porphyria
- AIP with severe neurovisceral symptoms, without cutaneous symptom

- Acute neurological presentation does not differ qualitatively among different forms of acute porphyria, including lead poisoning.

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- Due to their non-specificity, clinical features alone are not sufficient for confirm diagnosis of acute porphyric attack or to differentiate between various forms of acute porphyria.
- For this reason, an immediate (we recommend at onset of acute phase of disease) assessment and interpretation of laboratory biochemical tests:
- (determination and quantification of porphyrins and non-porphyrin precursor in biological samples) are mandatory for an accurate diagnosis, and hence for starting an appropriate treatment

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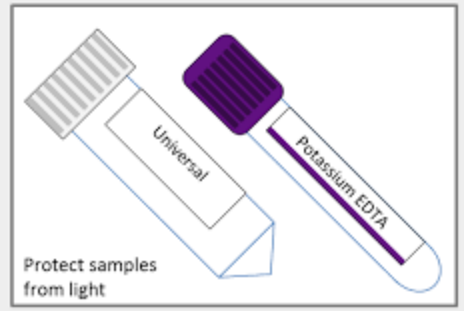
Diagnosing an acute porphyric attack — biochemical tests

Biochemical tests



- Step-1 ⟶⟶urinary excretion of non-porphyrin precursors:

I. δ-aminolevulinic acid (ALA)

II. Porphobilinogen (PBG)

- A fresh light-protected urine sample (Spot (single void) urine specimens) should be sent to a specialist laboratory (first-line test).
- In case of significant renal dysfunction, ALA and PBG levels should be measured in serum

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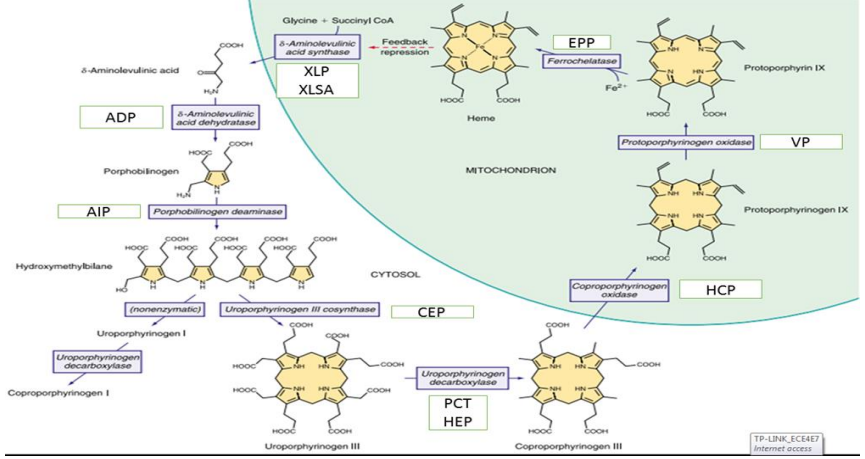
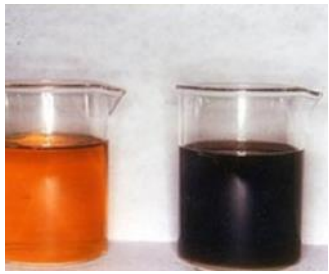
Biochemical tests



- Urinary PBG should be measured.
- Urinary PBG is always increased during acute attacks of AIP, HCP, and VP and is not increased in any other medical conditions.
- Therefore both sensitive and specific.
- Results from spot (single-void) urine specimens are highly informative because increases during acute attacks.(by using rapid (“bedside”) test kits)
- A 24-hour collection can unnecessarily delay diagnosis.
- Same spot urine specimen should be saved for quantitative of PBG (relative to cr) to confirm qualitative PBG
- ALA is often measured as well, but is usually less elevated than PBG in AIP, HCP, and VP.
- In ALA dehydratase porphyria (ADP), urinary ALA and porphyrins, but not PBG, are greatly elevated.
- Measurement of urinary porphyrins in addition to PBG is recommended to screen for acute porphyrias because PBG is often less elevated and returns to normal more rapidly in HCP and VP than in AIP.
- Porphyrin measurement alone should be avoided for screening, however, because it is often increased in many disorders other than porphyrias, such as liver diseases



- PBG is a colorless pyrrole and its measurement relies on formation of a violet pigment with para-dimethylaminobenzaldehyde (Ehrlich's aldehyde reagent).
- PBG must be separated from other urinary substances, principally urobilinogen, that also react with Ehrlich's aldehyde reagent.
- A kit for semiquantitative screening for elevated of PBG (Trace® PBG kit, Thermo Fischer Scientific) is reliable
- The Watson-Schwartz and Hoesch tests ,which involve initial addition of Ehrlich's reagent to urine, are less objective and less reliable, especially in inexperienced hands.
- uptodate

Biochemical tests

- These assays may miss diagnosis in some uncommon circumstances:

- a) In ALA-D porphyria or lead poisoning→↑ALA but not PBG
- b) Immediately treat with heme arginate (rapidly ↓ ALA and PBG)
- c) In HCP and VP, ↑ ALA and PBG may be more transient
- d) In high urinary bilinogen excretion (due to cross-reaction with p-dimethylaminobenzaldehyde)

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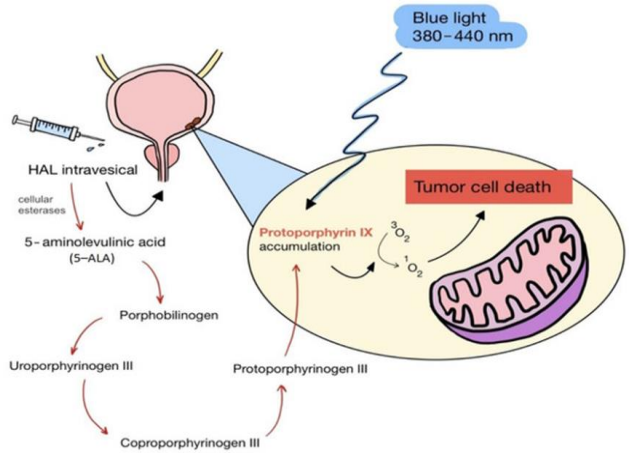
Isolated urinary ALA increase may also arise from:



a) Oral ALA ingestion, used in photodynamic localization and treatment of variety of malignant lesions

b) Hereditary tyrosinemia type I (Succinylacetone is structurally similar to ALA, inhibits ALAD)→can symptoms resembling acute porphyria

c) lead exposure (Inhibition of erythrocyte ALAD activity)

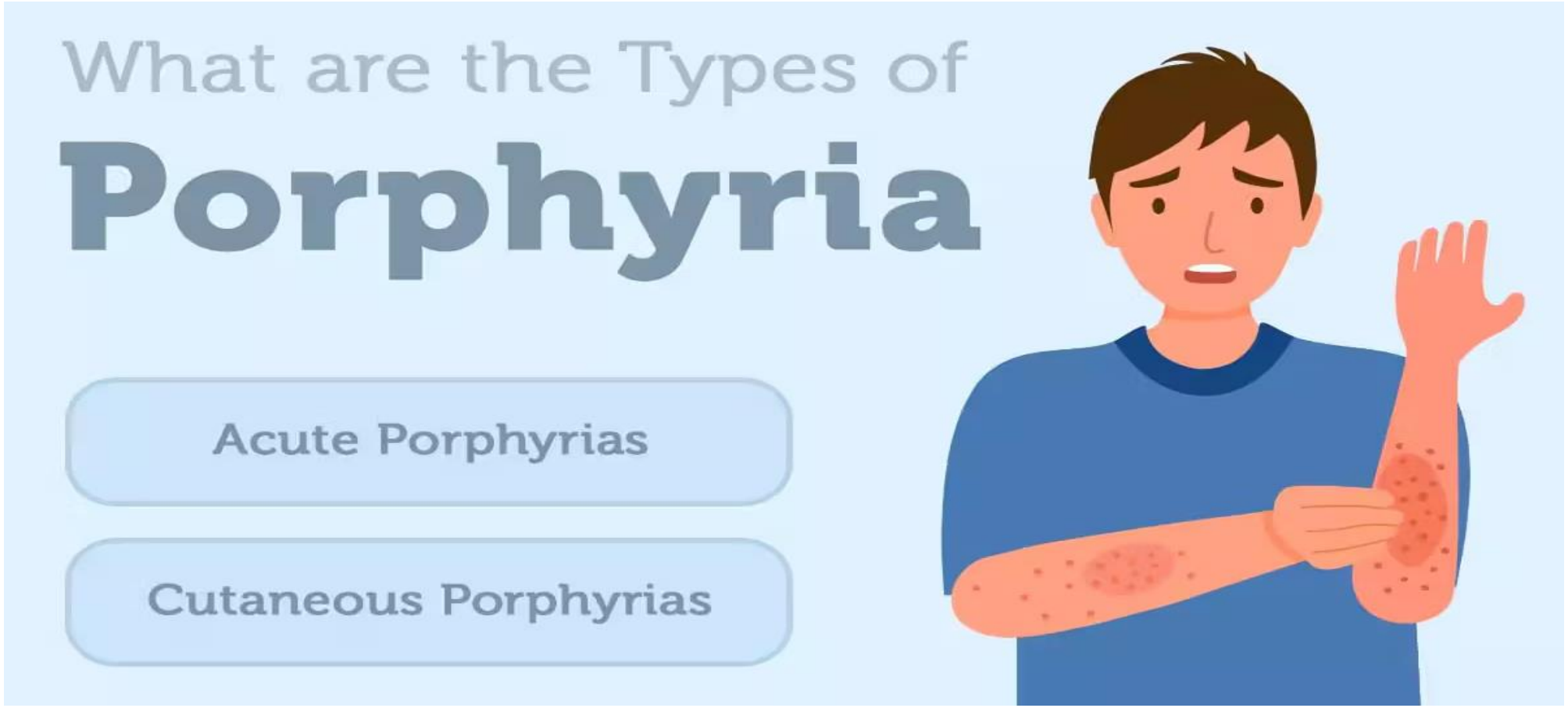
- Clinicians should confirm ALA-dehydratase porphyria or lead intoxication by using also enzymatic and molecular methods.

- δ-aminolevulinic acid — Normal urinary excretion ALA is <7 mg/24 h (53 μmoles/24 hours).
- In attack of AIP, urinary ALA is markedly elevated, >10 times upper limit of normal (25 to 100 mg/day).

- Porphobilinogen- Normal urinary excretion of PBG is <2 to 4 mg/24 h (<9 to 18 micromoles/24 hours)
- In attack of AIP, urinary PBG is markedly elevated, at least 5 to 10 times upper limit of normal (50 to 200 mg/day; 220 to 880 μmoles/day).

- uptodate

Step 2 — definition of the kind of acute porphyria



After diagnosing an acute porphyric attack, it is mandatory to define kind of acute porphyria

- AIP, VP, and HCP may be readily differentiated, if clinically overt, by a group of biochemical tests including:

A. Assessment of urine, plasma, and fecal porphyrin patterns (should samples collected distant from heme arginate therapy)

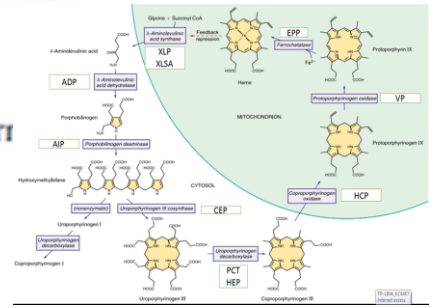
B. Fluorescence plasma patterns

- These tests may also be used to identify rare cases of dual porphyrias (deficiencies of 2 enzymes of heme pathway)

Presentation:	Porphyrias	Tests to order	Sample
Acute symptoms	AIP	1. Urine Porphyrin Precursors Screen & Quantitation	Random (50 ml) or 24-h with Tartaric acid
Acute symptoms + skin lesions (may occur independently)	VP HCP	2. Feces Porphyrins Screen & Quantitation	Random
Skin lesions	PCT CEP EP	1. Urine Porphyrin Precursors Screen & Quantitation 2. Feces Porphyrins Screen & Quantitation 3. Urine Porphyrins Screen & Quantitation 4. RBC Porphyrins Screen & Quantitation	Random (50 ml) or 24-h with Tartaric acid Random Random (50 ml) or 24-h with Na_2CO3 Lavender-top (EDTA) blood; need Hct

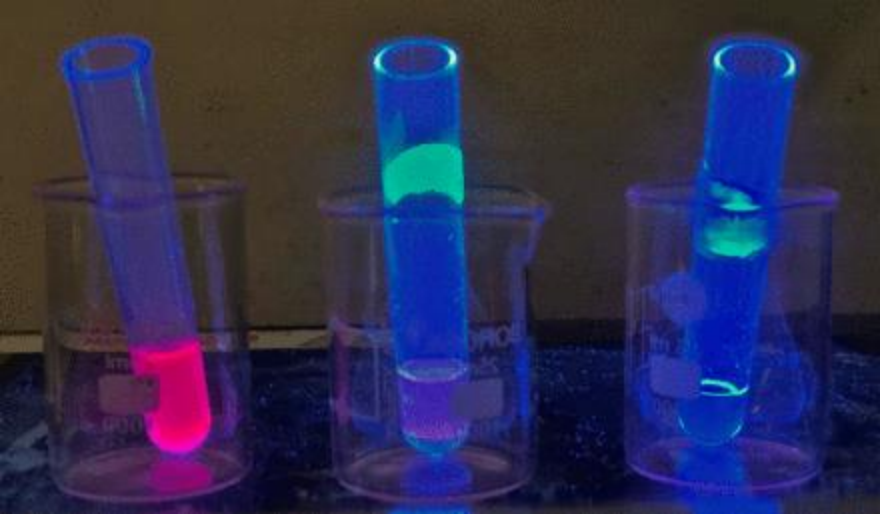
Table 1
Main clinical and biochemical features of acute porphyrias.
(in bold the most characteristic biochemical features for each kind of acute porphyria).

Disease	Clinical features	Plasma fluorescence	Erythrocyte	Urine	Stool
Acute intermittent porphyria (AIP)	-Acute neurovisceral attacks, neuropathy, or both -No skin lesions	Emission peak at wavelength of 618 ± 2 nm*	–	**Increased urinary levels of ALA and PBG (PBG > ALA)** (higher during acute attacks) **-Increased urinary porphyrins** (URO >> COPRO)**	-Normal
Hereditary coproporphyria (HCP)	-Acute neurovisceral attacks, neuropathy, or both -Blister skin lesions and skin fragility (in 30% of patients)	Emission peak at wavelength of 618 ± 2 nm*	–	-Increased urinary levels of ALA and **PBG** (**PBG > ALA**) mostly only during acute attacks **-Increased urinary porphyrins (URO and COPRO)**	**-Increased faecal porphyrins** (COPRO ≫ PROTO, with Copro III prevalence)
Variegate porphyria (VP)	-Acute neurovisceral attacks in 20–30% patients (50% with blisters or skin lesions)	**Emission peak at wavelength of 626 ± 2 nm**	–	-Increased urinary levels of ALA and **PBG** (**PBG > ALA**) mostly only during acute attacks **-Increased urinary porphyrins (COPRO prevalence)**	**-Increased faecal porphyrins (PROTO >> COPRO, with Copro III prevalence)**
ALA dehydratase deficiency porphyria (ALAD-P)	-Acute neurovisceral attacks, neuropathy, or both -No skin lesions	Emission peak at wavelength of 618 ± 2 nm*	**-High Total erythrocyte protoporphyrins (High ZnPP)**	**-Increased urinary levels of ALA (ALA >> PBG)** -Increased urinary porphyrins (COPRO; prevalence of COPRO III)	-Normal
Lead Poisoning (plumboporphyria)	-Acute neurovisceral attacks, neuropathy, or both **-Lead exposition (incidental, professional)** **-Microcytic anaemia**	Emission peak at wavelength of 635 nm	**-High total erythrocyte protoporphyrins (High ZnPP)**	**-Biochemical features resembling ALAD-P (see above) (prevalence of Copro I)** **-High level of lead in serum and urine**	-Norı

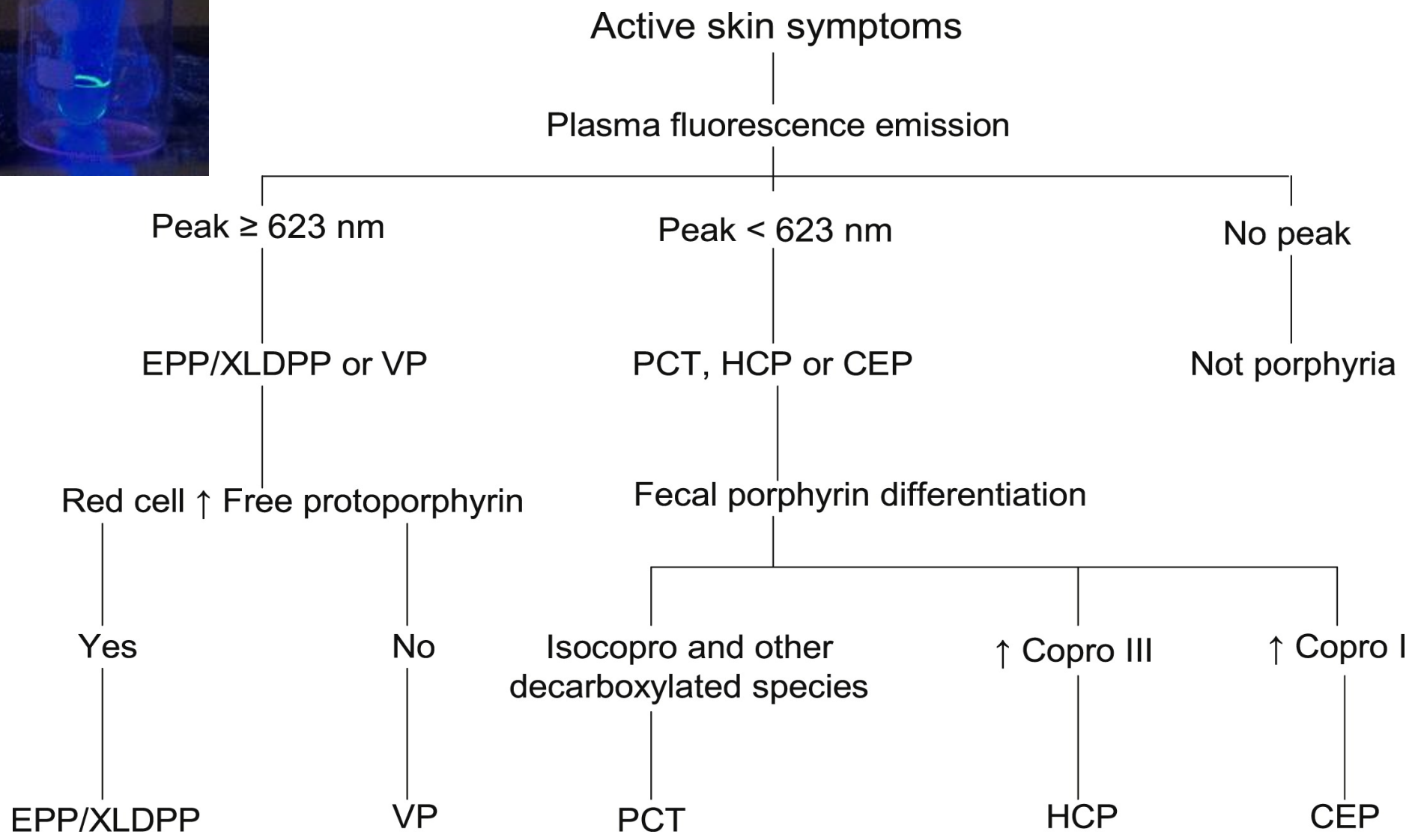


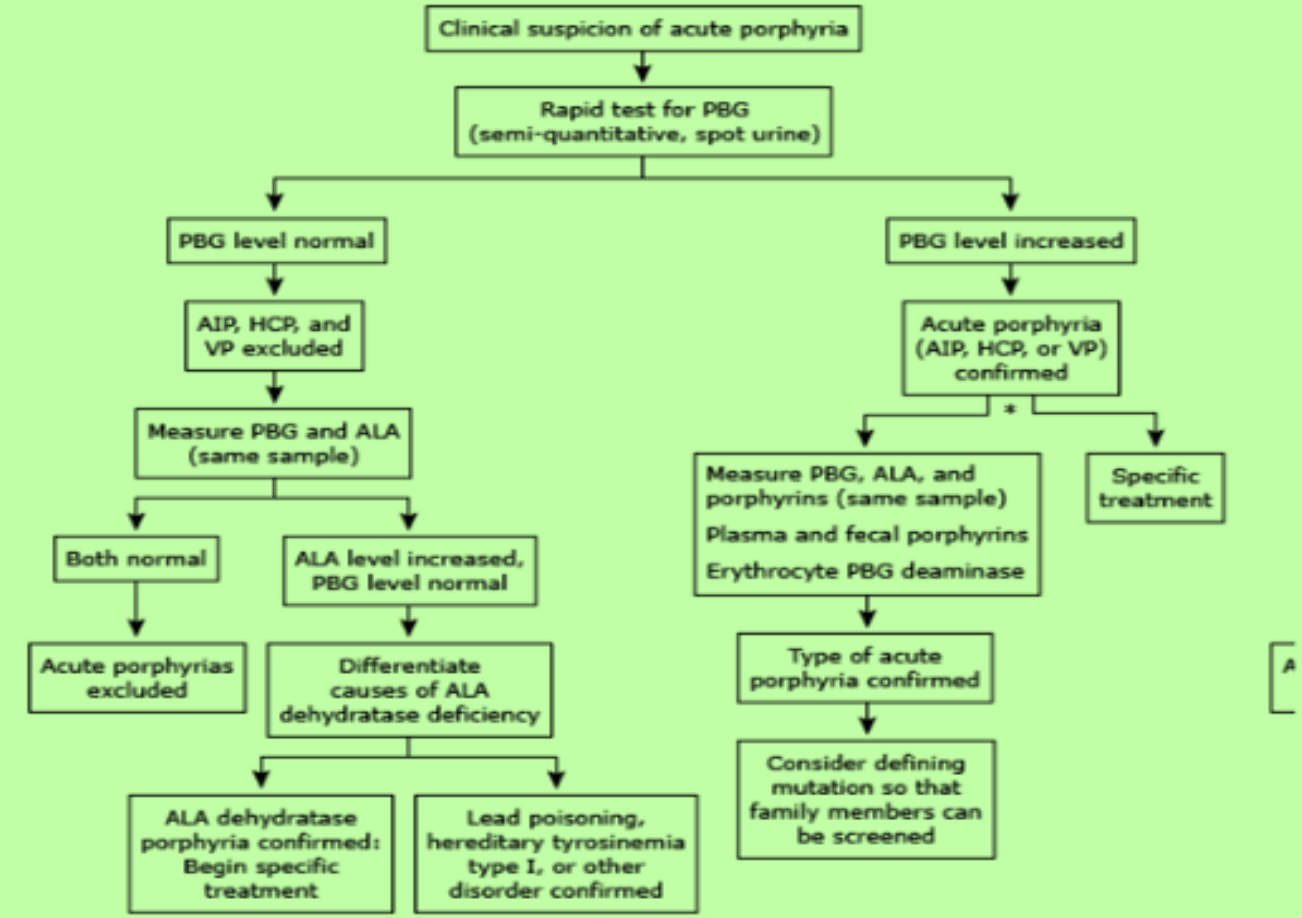
Abbreviations: ALA = delta amino-levulinic acid; PBG = Porphobilinogen; URO = Uroporphyrins; COPRO = Coproporphyrins; PROTO = Protoporphyrins; ZnPP = Zinc Protoporhyrins. *described in literature, but not frequent; **sometimes COPRO may be prevalent.

References: Ventura E. and Rocchi E., in: Le Porfirie; in: Teodori 2000. Trattato di Medicina Interna (2000); Hindmarsh JT. Clin Chim Acta. 2003; 333:203-7; Deacon A.C. and Elder G.H. J Clin Pathol. 2001. 7:500-7. EPI/Epnet (http://www.porphyria-europe.com).



Fluorescent pink color discoloration of urine under ultraviolet light examination in acute hepatic porphyria

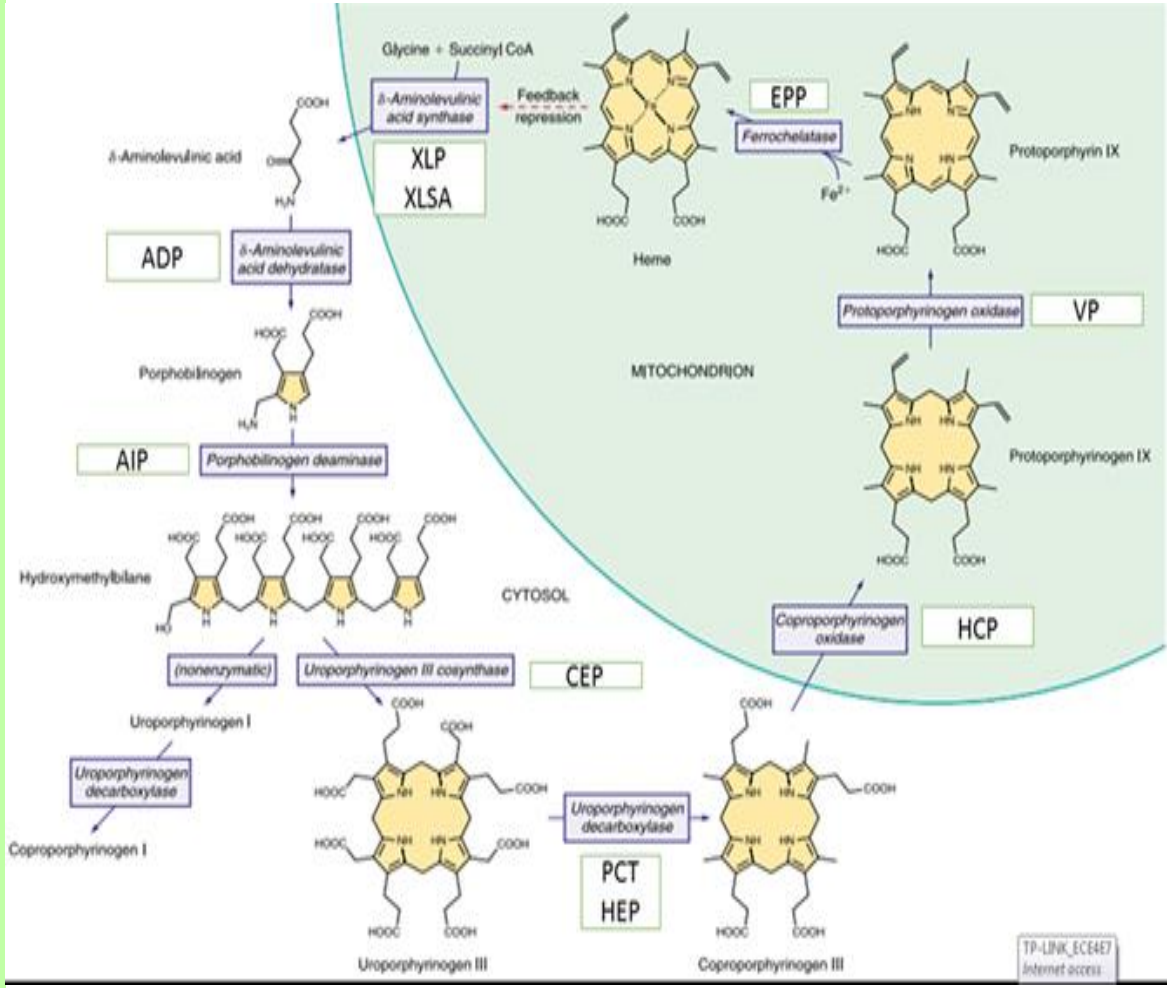




This decision tree shows the recommended laboratory evaluation of patients with concurrent symptoms suggesting an acute porphyria, indicating how the diagnosis is established or excluded by biochemical testing and when specific therapy should be initiated.

This schema is applicable only to symptomatic patients who may be having an acute attack. Levels of ALA and porphobilinogen may be less increased in HCP and VP and decrease more quickly with recovery than in AIP; urine porphyrins may remain increased, but are subject to nonspecific increases. Mutation detection provides confirmation and greatly facilitates detection of relatives with latent porphyria.

PBG: porphobilinogen; ALA: 5-aminolevulinic acid; ADP: ALA dehydratase porphyria; AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria; ALAD: ALA dehydratase; PBGD: PBG deaminase; CPO: coproporphyrinogen oxidase; PPO: protoporphyrinogen oxidase.



Excretion patterns for porphyrins and porphyrin precursors and other laboratory findings in the human porphyrias

Porphyria	Urine	Stool	Erythrocytes	Plasma
ADP	ALA, coproporphyrin III	*	Zinc protoporphyrin	ALA*
AIP	ALA, PBG, uroporphyrin	*	Decreased PBGD activity (most cases) *	ALA, PBG* [~620 nm] •
CEP	Uroporphyrin I; coproporphyrin I	Coproporphyrin I	Uroporphyrin I; coproporphyrin I	Uroporphyrin I, coproporphyrin I [~620 nm] •
PCT and HEP	Uroporphyrin, heptacarboxyl porphyrin	Heptacarboxyl porphyrin, isocoproporphyrins	Zinc protoporphyrin (in HEP)	Uroporphyrin, heptacarboxyl porphyrin [~620 nm] •
HCP	ALA, PBG, coproporphyrin III	Coproporphyrin III	*	Δ [~620 nm] •
VP	ALA, PBG, coproporphyrin III	Coproporphyrin III, protoporphyrin	*	Porphyrin-peptide conjugate [~626 to 628 nm] •
EPP	◇	Protoporphyrin*	Free protoporphyrin §	Protoporphyrin [~634 nm] •

ADP: ALA dehydratase porphyria; AIP: acute intermittent porphyria; CEP: congenital erythropoietic porphyria; PCT: porphyria cutanea tarda; HEP: hepatoerythropoietic porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria; EPP: erythropoietic protoporphyria; ALA: delta-aminolevulinic acid; PBG: porphobilinogen; PBGD: porphobilinogen deaminase; XLPP: X-linked protoporphyria.
* Porphyrin levels normal or slightly increased.
• Fluorescence emission peak of diluted plasma at neutral pH.
Δ Plasma porphyrins usually normal, but increased when blistering skin lesions develop.
◇ Urine porphyrins (especially coproporphyrin) increase only with hepatopathy.
§ Zinc protoporphyrin ≤5 percent of total in classic EPP, but 15 to 50 percent in variant form (XLPP).

zinc protoporphyrin

- For diagnosis of EPP and XLP:

1) Measurement of total erythrocyte protoporphyrin and, if total is elevated,
2) Fractionation of protoporphyrin in to metal-free and zinc-chelated forms

- Increases in erythrocyte total and zinc-chelated protoporphyrin occur in many other conditions, including:

- Iron deficiency
- lead poisoning
- Hemolysis
- Anemia of chronic disease
- Other erythrocyte disorders.

- Therefore diagnosis of EPP must be confirmed by showing a predominant increase in free and metal-free protoporphyrin.
- In XLP, both free and zinc protoporphyrin are elevated

- These tests remain mandatory in follow-up of disease during symptom-free periods, in order to evaluate efficacy of treatment and risk long-term organ complications (liver and kidney) in acute porphyrias.
- Evaluation of specific enzyme activities (assessed on erythrocytes, fibroblasts or liver tissue) may also be useful in some cases.

- Review Article. A challenging diagnosis for potential fatal diseases: Recommendations for diagnosing acute porphyrias

Classification of the human porphyrias as hepatic or erythropoietic and as acute or cutaneous, the affected enzymes, patterns of inheritance and their major biochemical features

Disease	Classification		Enzyme affected	Inheritance	Major biochemical findings*			
	Tissue site	Clinical features			Urine	Plasma	Erythrocytes	Feces
ADP	Hepatic •	Acute	ALAD	Autosomal recessive	ALA, coproporphyrin III	ALA, coproporphyrin III	Zinc protoporphyrin and low ALAD activity	
AIP	Hepatic	Acute	PBGD	Autosomal dominant	ALA, PBG, coproporphyrin		Low PBGD activity	
HCP	Hepatic	Acute and cutaneous	CPO	Autosomal dominant	ALA, PBG, coproporphyrin III			Coproporphyrin III
VP	Hepatic	Acute and cutaneous	PPO	Autosomal dominant	ALA, PBG, coproporphyrin III	Fluorescence peak at 626 nm		Coproporphyrin III and protoporphyrin
PCT	Hepatic	Cutaneous	UROD	Autosomal dominant Δ	Uroporphyrin and hepta-carboxyl-porphyrin	Uroporphyrin and hepta-carboxyl-porphyrin		Isocoproporphyrin
HEP	Hepatic •	Cutaneous	UROD	Autosomal recessive	Uroporphyrin and hepta-carboxyl-porphyrin	Uroporphyrin and hepta-carboxyl-porphyrin	Zinc protoporphyrin and low UROD activity	Isocoproporphyrin
CEP	Erythro-poietic	Cutaneous	UROS	Autosomal recessive	Uroporphyrin I and coproporphyrin I	Uroporphyrin I and coproporphyrin I	Uroporphyrin I and coproporphyrin I	Coproporphyrin I
EPP — classic form	Erythro-poietic	Cutaneous	FECH	Autosomal dominant		Protoporphyrin	Free protoporphyrin	Protoporphyrin
EPP — variant form	Erythro-poietic	Cutaneous	ALAS2	X-linked recessive		Protoporphyrin	Free and zinc protoporphyrin	Protoporphyrin

ADP: ALA dehydratase porphyria; AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria; PCT: porphyria cutanea tarda; HEP: hepatoerythropoietic porphyria; CEP: congenital erythropoietic porphyria; EPP: erythropoietic protoporphyria; ALAD: ALA dehydratase; PBGD: porphobilinogen deaminase; CPO: coproporphyrinogen oxidase; PPO: protoporphyrinogen oxidase; UROD: uroporphyrinogen decarboxylase; UROS: uroporphyrinogen III synthase; FECH: ferrochelatase; ALAS2: ALA-synthase 2; ALA: delta-aminolevulinic acid; PBG: porphobilinogen.

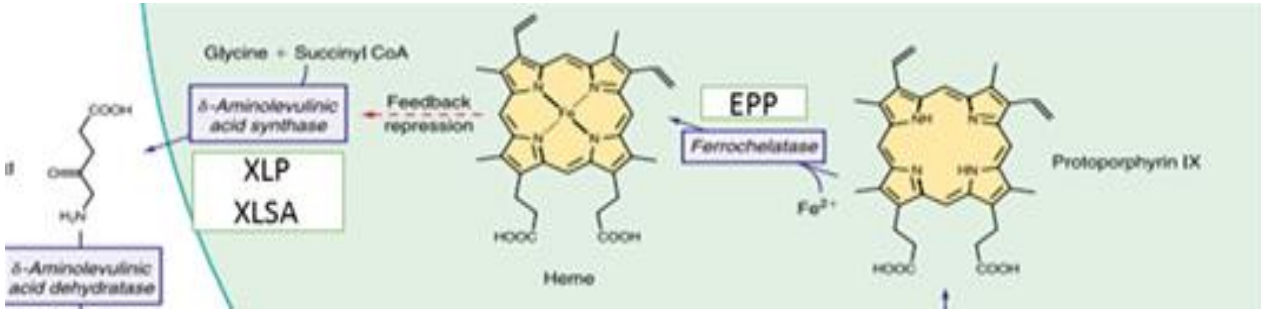
* Increases of importance for diagnosis in most cases.

• These hepatic porphyrias also have erythropoietic features, including increases in erythrocyte zinc protoporphyrin.

Complication

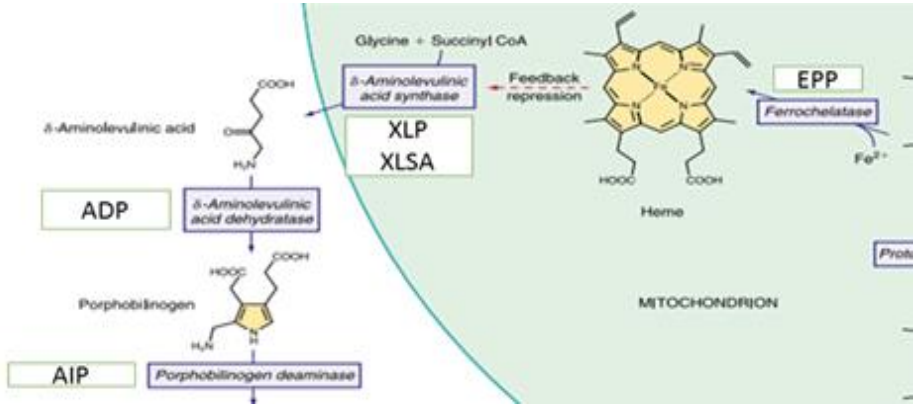
- EPP :
  - Myelodysplastic or myeloproliferative disorders
  - Chronically ↑ LFT or rapidly progressive hepatic failure.
  - Billiary stone
- AIP :
  - chronic liver disease.
  - Risk of hepatocellular carcinoma 60- to 70-fold after age 50, even in asymptomatic individuals.
- PCT:
  - Pseudoscleroderma, calcification of skin and subcutaneous tissue
  - advanced liver disease and hepatocellular carcinoma
- Liver imaging and serum α-fetoprotein determination may be advisable in all PCT with cirrhosis or advanced fibrosis at 6-month intervals
- HCP:
  - Concomitant liver diseases may increase porphyrin retention and photosensitivity.
  - Risk of hepatocellular carcinoma is increased.

Treatment experience with EPP and XLP



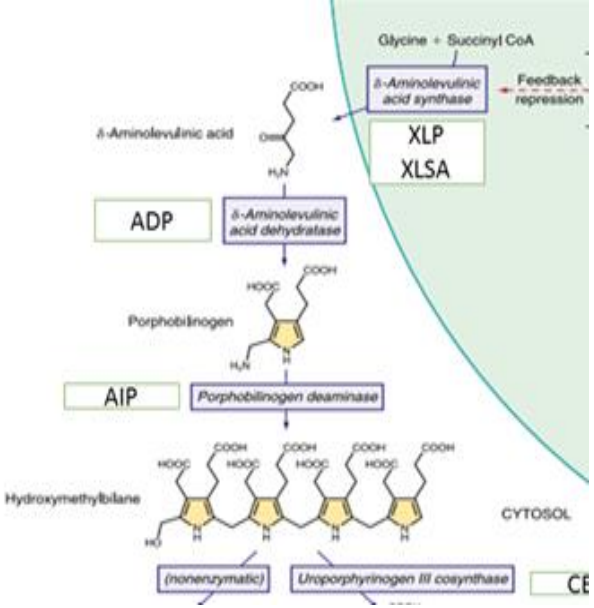
- Exposure to sunlight should be avoided
- Beta-carotene, oral cysteine, vitamin C have no proven efficacy.
- High doses of cimetidine were effective in reducing symptoms in 3 children EPP
- Increasing skin melanin by narrow-band UV-B phototherapy
- Afamelanotide, synthetic analog of melanocyte-stimulating hormone, darkened skin
- Dersimelagon, orally selective melanocortin-1 receptor (MC1R) agonist , increases skin melanin.
- Drugs or hormone that impair hepatic excretory function should be avoided.
- Iron deficiency should be corrected, particularly in XLP.
- Vitamin D and hepatitis A and B vaccination are recommended.

Treatment experience with ADP



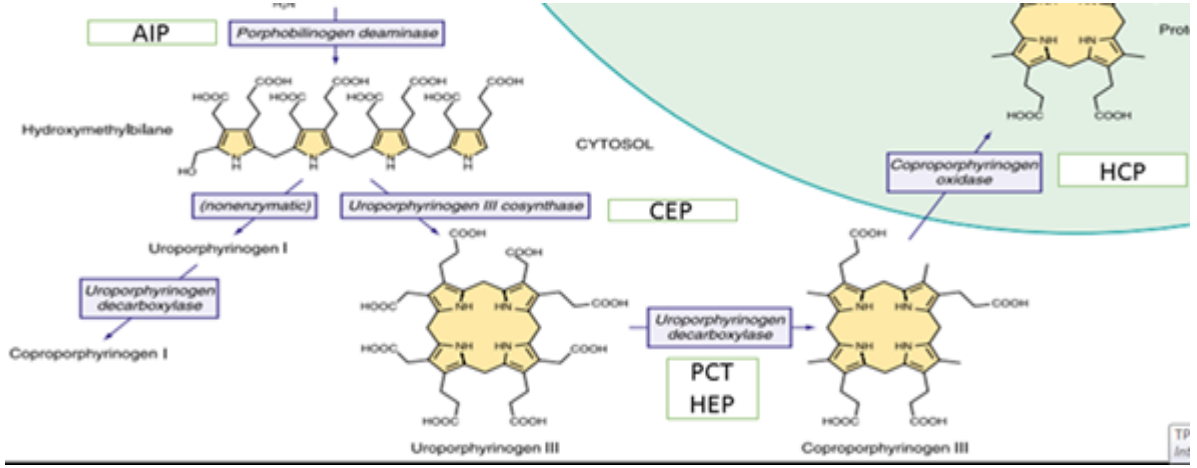
- Is limited but is similar to other acute porphyrias.
- Glucose seems to have minimal effectiveness but may tried for mild symptoms.
- Hemin therapy
- Hemin is effective in porphyria-like symptoms with tyrosinemia and can reduce urinary ALA and coproporphyrin in lead poisoning.
- Avoidance of drugs that are harmful
- Liver transplantation was not effective in child with severe disease.
- In a recent report, weekly blood transfusions and hydroxycarbamide used in addition to heme-arginate to suppress erythroid heme synthesis

Treatment experience with AIP



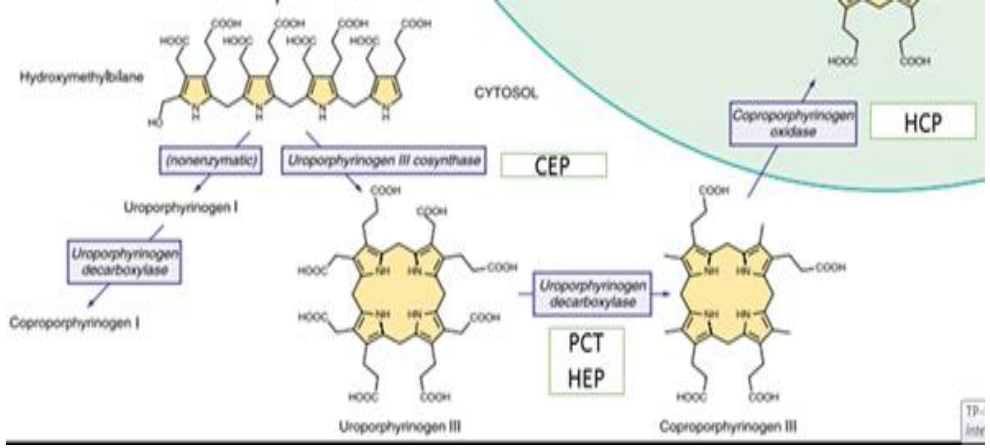
- Pain usually requires opioid; low risk addiction after recovery from acute attack.
- Ondansetron or promethazine for nausea and vomiting
- short-acting benzodiazepines for anxiety and restlessness.
- β-Adrenergic blocking for tachycardia and HTN but may hazardous in patients hypovolemia and cardiac failure
- IV hemin is treatment of choice for most acute attacks of porphyria.
- Standard regimen of hemin for treatment of acute porphyric attacks is 3-4 mg/kg/day for 4 days.
- Givosiran, an ALAS1-directed interfering RNA therapeutic, is effective for preventing frequent attacks
- Liver transplantation is effective in severe AIP who refractory to pharmacologic therapy.
- Gabapentin, pregabalin, levetiracetam, and vigabatrin are considered safe or probably safe, and clonazepam is probably less harmful than phenytoin, barbiturates, or valproic acid.
- Control of HTN is important and may help prevent chronic renal impairment and renal transplantation

Treatment experience with CEP



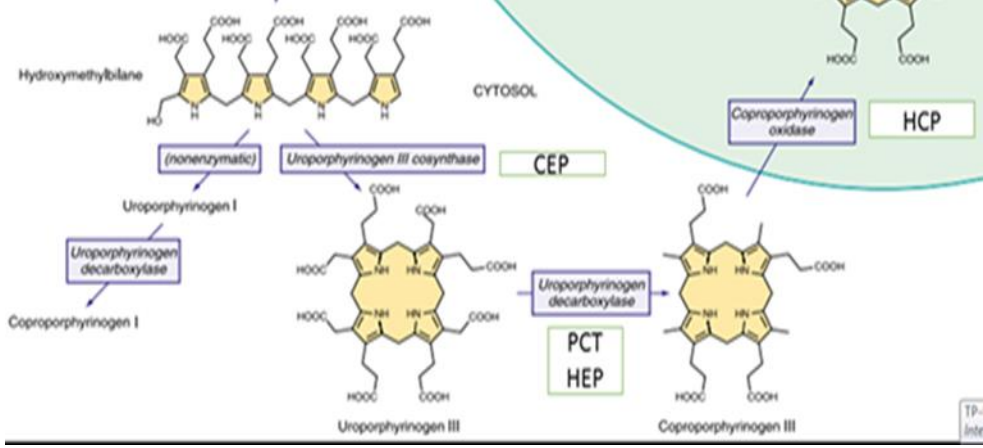
- Avoid sunlight exposure is essential
- Minimizing skin trauma and prompt treatment of any cutaneous infections are essential.
- Sunscreen lotions and beta-carotene are of little benefit.
- Transfusions to achieve Hgb sufficient to significantly suppress erythropoiesis for reducing porphyrin and photosensitivity.
- Concurrent deferoxamine to reduce iron overload and hydroxyurea to suppress erythropoiesis
- Splenectomy reduces hemolysis and transfusion requirements in some patients.
- Iron restriction by phlebotomy or iron chelators may improve photosensitivity in CEP by decreasing ALAS2 activity and porphyrin production.
- Most effective treatment is marrow stem cell transplantation in early childhood, which has greatly reduced porphyrin and photosensitivity and increased long-term survival.

Treatment experience with PCT



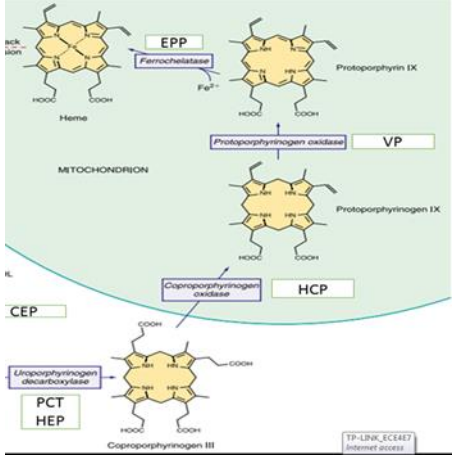
- Two specific and effective forms of treatment, phlebotomy and low dose hydroxychloroquine
- Susceptibility factors should be removed when possible.
- Use of alcohol, estrogens (in women), and smoking should be stopped, and patients tested for HCV, HIV, and HFE pathogenic variants.
- Susceptibility factors and degree of iron overload, as assessed by serum ferritin, can influence choice of treatment.
- Infusions of deferoxamine, an iron chelator, when phlebotomy is contraindicated
- Low-dose of hydroxychloroquine (or chloroquine)When phlebotomy is contraindicated

Treatment experience with HEP



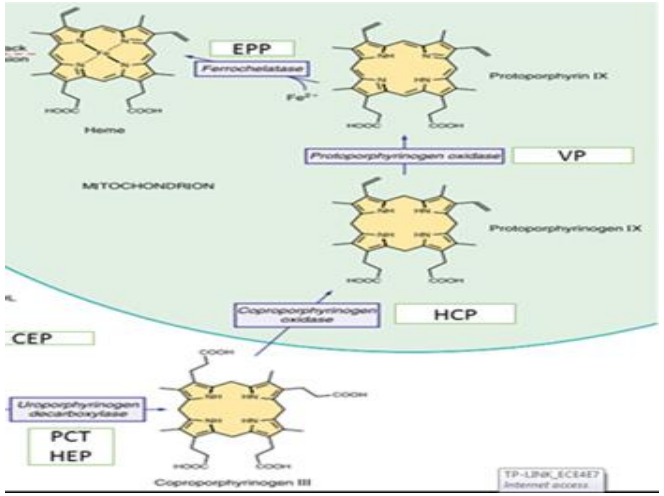
- Avoiding sunlight exposure is most important in HEP, as in CEP.
- Oral charcoal was helpful in severe case with dyserythropoiesis.
- Phlebotomy has shown little or no benefit.

Treatment experience with HCP



- Acute attacks of HCP are treated as in AIP, includes IV hemin
- Identifying and avoiding precipitating factors.
- Phlebotomy and chloroquine are not effective.
- GnRH analogs can effective for prevention of cyclic attacks.
- Prognosis is generally better than in AIP.
- Givosiran, an siRNA therapeutic agent, has been approved for prevention of acute attacks in all acute hepatic porphyrias, although experience in HCP is limited.
- Prevention and genetic counseling are same as in other acute porphyrias

Treatment experience with VP



- Acute attacks are treated as in AIP
- Hemin is beneficial for acute attacks but not for cutaneous symptoms.
- Light protection is important ,using long-sleeved clothing, gloves, a broad-brimmed hat, and sunscreen preparations
- Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and protection.
- Phlebotomy and chloroquine are not effective.
- Surprisingly, oral activated charcoal was reported to increase porphyrin and worsen skin manifestations.

Thank you for your attention