Porphyrias

تبييض وحوسبة : عبادة العايد
تدقيق : عمران يونس

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واطلب من الله ان يعينك على دراسة هذه المحاضرة وفهمها

Introduction

-The porphyrias are caused by deficiencies of enzymes involved in heme biosynthesis which lead to blockade of the porphyrin pathway and subsequent accumulation of porphyrins and their precursors.

- Either genetic (autosomal dominant, autosomal recessive and X-linked) or acquired. (Note 1 next slide)

- Heterozygotes (one gene is mutated and other are normal) are asymptomatic in between acute attacks.

- Classified depending on site of overproduction and accumulation of porphyrin, overlapping features common

Hepatic

↓

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

Erythropoietic

↓

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

1- Cell damage

2- Hemolytic anemia

. Note : 1* This diseases - even now - overlaping features of porphyrias ,so it is very difficult to diagnosed except by genetic study because it is highly overlaping and has diversity in genetics (autosomal receessive , autosomal dominant , acquired)

** there are two enzymes lead to acquired porphyrias :

1. ALA dehydratase ---> by lead (Pb+2)
2. Ferrochelatase ----> by lead (Pb+2)

Both lead to acquired porphyrias .

Note :2 Inhibition of any enzyme lead to accumulation of intermediates preceedes this enzyme , so porphyrias also calssified according to site of accumulation of porphyria as follow :

.1 hepatic = the enzyme which is deficient is in the liver , also the intermediae which is accumulated also in liver....

.2 Erythropoietic = accumulation subcutaneously , so there will be attraction of more UV rayes = free radicals , so most of manifistations of erythropoietic porphyrias related to skin

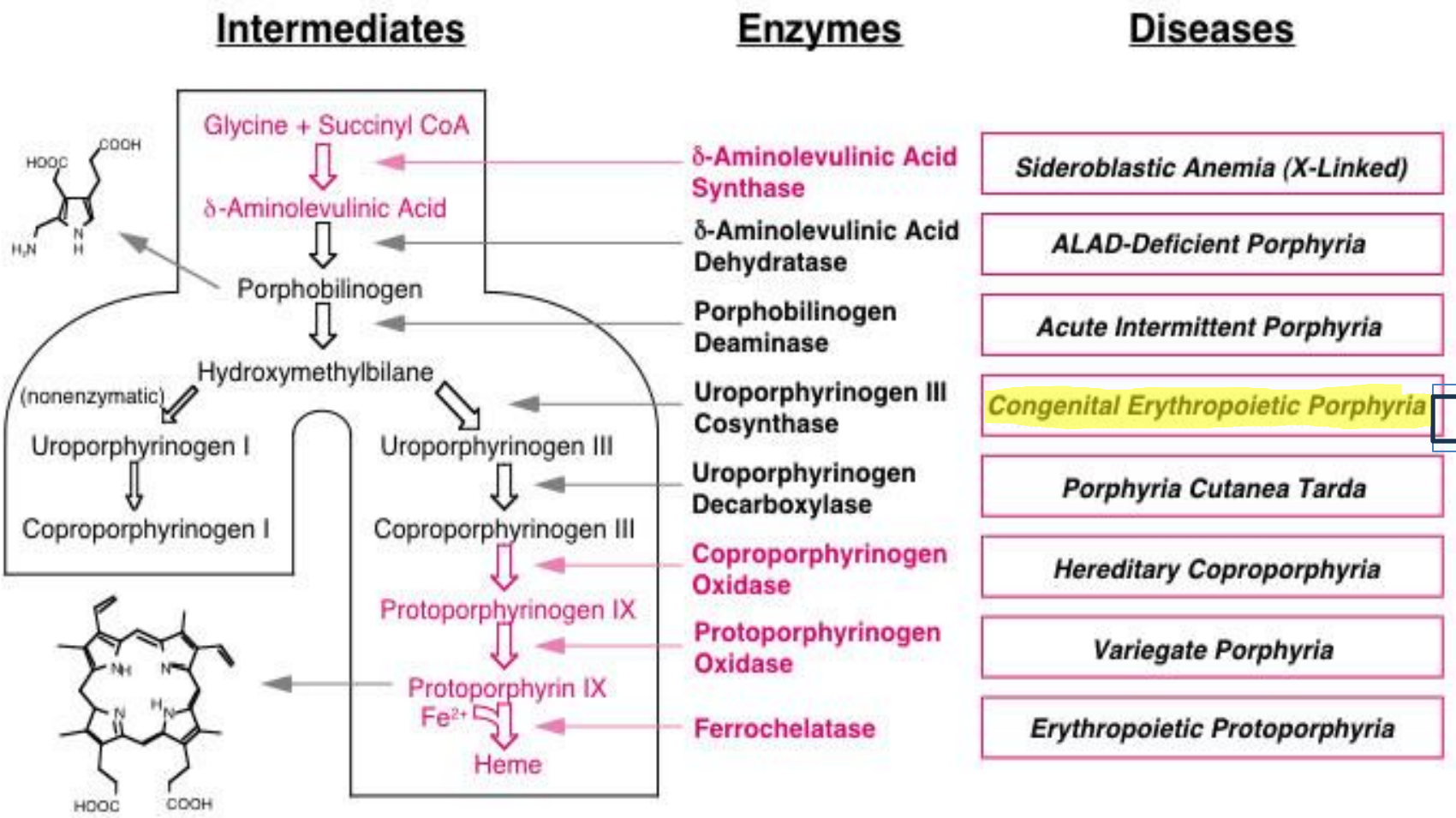
Note:* 3
Neurological manifastations :

Because of accumulation of intermediate in the viscera which lead to excitation of the nerve endings , so sever pain occur .
This sever pain in this case can't be stopped except by morphins.

Autosomal recessive -→ both genes should be mutated for the occurance of manifistations.

Autosomal dominant -→ only one gene are required to appear of manifestations.

Heme Synthesis Pathway



Note 4

Note : 4

- ALL porphyrias are related to deficiency in enzyme itself , but in case of **congenital erythropoietic porphyria** ,the deficincy are in co-enzyme not in enzyme itself .
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- #Remember : Uroporphyrinogen III synthase enzyme reaction lead to flipping over in ring number 4 in the heme structure . the deficincy are in co-enzyme not in enzyme itself .

Classification of the Porphyrias

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

Porphyria categories

A- Bone Marrow

- Erythropoietic protoporphyria
- Congenital erythropoietic porphyria

Congenital erythropooetic porphyria & Erythropoietic protoporphyria .... Both are erythropoietic (in bone marrow) ...You can notice that from the name of disease .
The rest of diseases are hepatic.

B- Liver

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

Hepatoerythropoietic porphyria :

It is mixed chronic porphyria , deficincy of the enzyme and accumulation of intermediates not in bone marrow only and not in liver only but occur in both , and it is the only type its effects are neurological & cutaneous.

Overview of the four acute porphyrias

- Four acute porphyrias cause acute, self-limiting attacks that lead to chronic and progressive deficits
- Symptoms of acute attacks increase the potential for misdiagnosis.
- Acute porphyrias are clinically indistinguishable during acute attacks, except the neurocutaneous porphyrias (variegate porphyria and hereditary coproporphyria) can cause dermatologic changes
- Acute attacks lead to an increase in PBG and ALA which can be detected in urine
- Diagnosis is difficult because of :

1) variable clinic course (some are cutaneois , some neurological , some both)
2) lack of understanding about diagnostic process,
3) and lack of a universal standard for test result interpretation

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

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

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

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

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

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

Diagnosis

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

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

Note :5 Correct diagnosis of porphyria cases depend on :

.1 To a little bit clinical picture
.2 To a little bit laboratory investigations
But you will not be sure at 100% of your diagnosis , so:
.3 Genetic study , on the 8 genes involving in heme synthesis.

Note : 6

Laboratory investigations some times will be precursors which are intermediates in the heme synthesis pathway.

But in the case of (porphyria cutanea tarda) the diagnostic biomarkers which seen will be variable (diffrent) which are ... (It is the only one give diffrent intermediates which are not intermediates from heme synthesis pathway.

(7- carboxylate porphyria & isocopropophyrin)

Acute intermittent porphyria

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

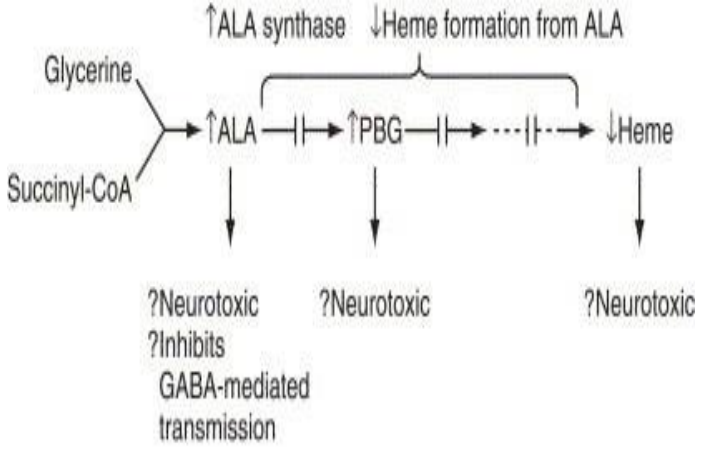
Note 7 next slide

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

Treatment:

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

Note 8 next slide



Note : 7

female which takes contraceptive pels , and without deficincy of PBG deaminase enzyme it may has some of symptoms which are related to this disease (symptoms which related to exacerbating of this disease)
Which known as (pseudo porphyria) .
So we have to avoid using the contraceptive pels if the patient is diagnosed with acute intermittent porphyria , because in this case the treatment will not be effective , and the presence of menstrual hormones will cause exacerbation of the case .

Note : 8

Aim of both is to inhibit the ALA synthase enzyme .
Heme is the end product of the heme synthesis pathway and it has inhibitory regulatory effect upon the trancritpion of genes encoding ALA synthase enzyme ..
Also glucose , during catabolism of glucose as source of energy , some intermediates in glycolytic pathway and citric acid cycle can inhibit the synthesis of ALA synthase enzyme , which are considerd as genetic level regulation of ALA synthase enzyme .

We use both together to make sure that the reaction of ALA synthase enzyme will be inhibited , and this because of the sever pain resulting from the irritation of the nerve endings because you will not continue to give morphin for patient to avoid addection .

Although this disease are genetic disorder , wherease we cann't treat genetic disorders to a definite line of treatment , we have to make gene therapy or stem cell therapy .

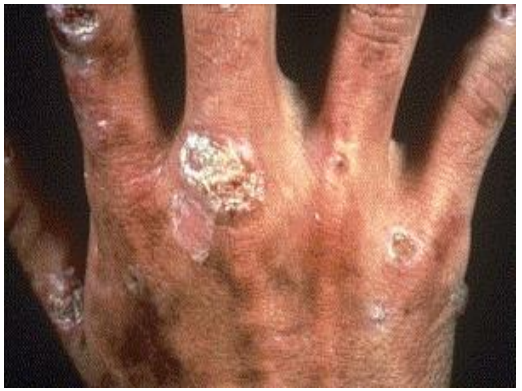
Porphyria cutanea tarda

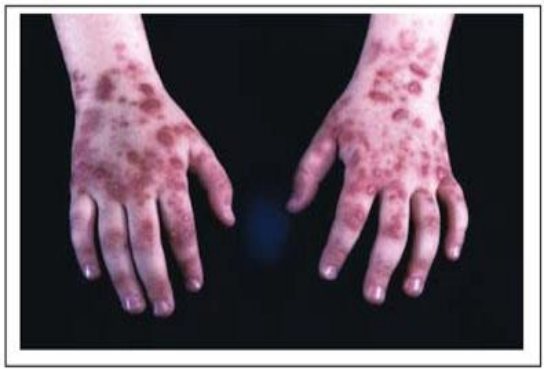
- Most common porphyria which causes skin manifestations
- Deficiency of hepatic urodecarboxylase
- Cutaneous photosensitivity → fluid filled vesicles on sun exposed areas, friable skin, wounds heal slowly and hyperpigmentation on face
- No neurologic manifestations
- Higher incidence of hepatocellular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

More frequent among females.

Treatment:

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





Note : 9

Estrogen and menstrual hormones may cause porphyrias manifestations which called (pseudo porphyria) .

But on the other hand , pseudo porphyrias not only from estrogen or menstrual hormones , some persones may have manifestations of porphyria cutanea tarda after taking aspirin or tetracyclines , but it is only skin manifestations without any change in serum and urin and no intermediates will be excreated with urine.

Erythropoietic protoporphyria

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

Congenital erythropoietic porphyria (Gunther's disease)

- It is a very rare autosomal recessive disorder.
- Patients usually present during infancy and rarely present in adult life with milder forms.
- It is caused by elevation of both water-soluble and lipid-soluble porphyrin levels due to deficiency of uroporphyrinogen III Cosynthase.

Clinical features

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

Treatment

- Superactivated charcoal - Hypertransfusion
- Splenectomy - Bone marrow transplantation

Pseudoporphyria

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

Neurotoxicity mechanisms

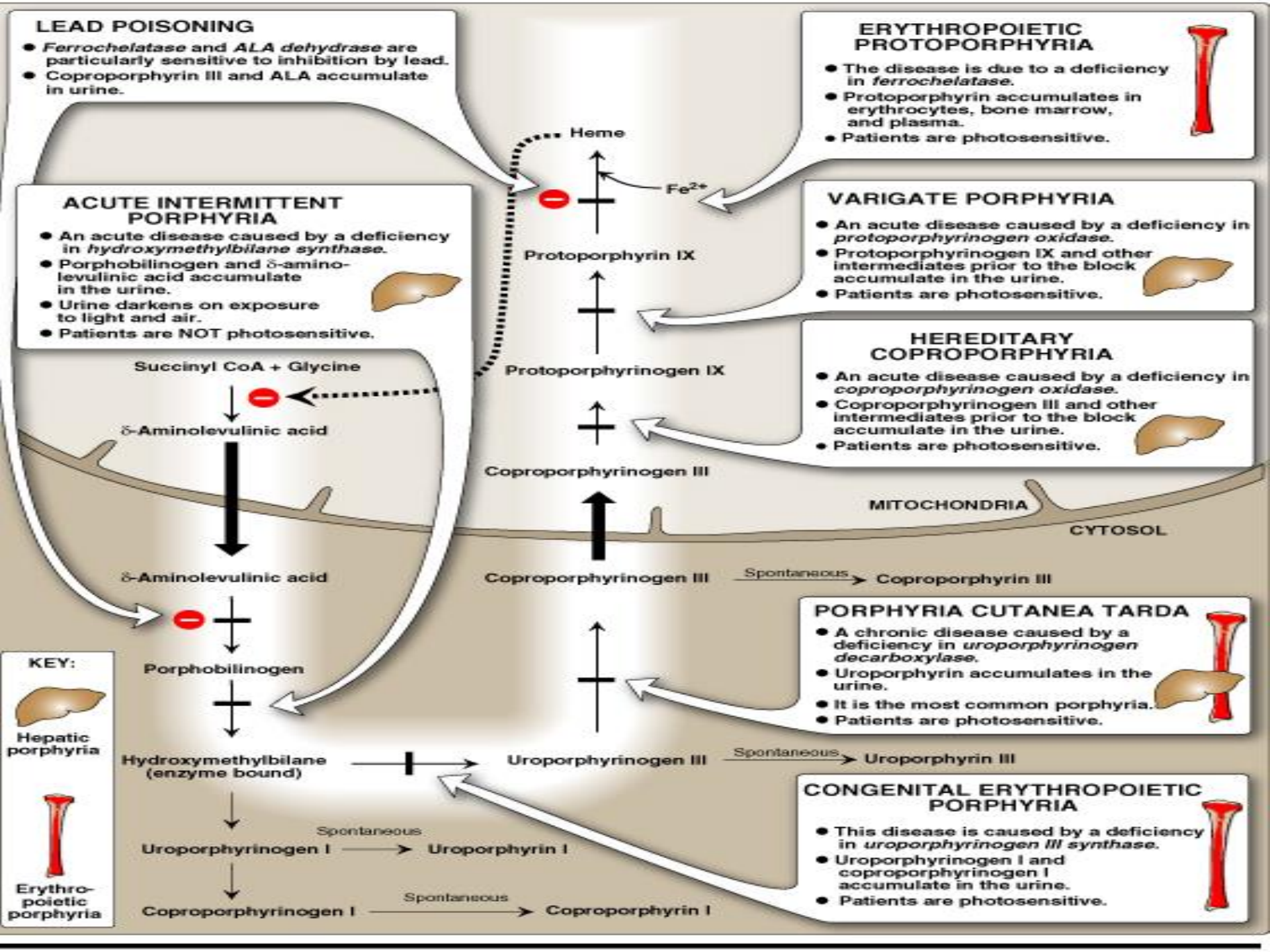
- Most current thinking focuses on accumulations of toxic metabolites.
- ALA and PBG are neurotoxins.
- ALA may be a false transmitter for GABA, it also blocks one of ATPases (perhaps a sodium pump).
- Another hypothesis: unsaturation of hepatic tryptophan pyrrolase secondary to liver heme deficiency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

Note 10 next slide

Note : 10

Heme are not found only in hemoglibin , myglobin & cytochromes , there are another enzymes which contain heme (peroxidase , catalse , tryptophan pyrrolase)
The tryptophan pyrrolase enzyme is important , because it work on tryptophan , which are precursore of 2 neurotransmittes excitatory in the CNS which are (serotonin & melatonin)
Also it convert tryptophan into niacin which produce NAD+ & NADP+ which are improtant in producing energy .

So if it not saturated with heme , it will be non functional , so its reactions affected and affect CNS activity.


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

ما هي الاشياء التي تكشف لك مكانك في عبودية الله ؟؟

قال ابن القيم رحمه الله في مدارج السالكين :

" وأما معرفة الزيادة والنقصان من الأيام فإنها تستقيم بثلاثة أشياء : **سماع العلم ، وإجابة داعي الحرمة ، وصحبة الصالحين ، وملاك ذلك كله خلع العادات .**
يعني أن السالك على حسب علمه بمراتب الأعمال ، ونفائس الكسب ، تكون معرفته بالزيادة والنقصان في حاله وإيمانه ، وكذلك تفقد إجابة داعي تعظيم حرمات الله من قلبه هل هو سريع الإجابة لها ، أم هو بطيء عنها ؟ فبحسب إجابة الداعي سرعة وإبطاء تكون زيادته ونقصانه . "

اذا احببت سماع كلام قيم حول هذه الفكرة ومناقشة هذا النص اليك الرابط التالي 👇😊

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