Inborn Errors of Metabolism

Shuzan Ali Mohammed
Medical Biochemistry & Molecular Biology
Faculty of Medicine- Benha University

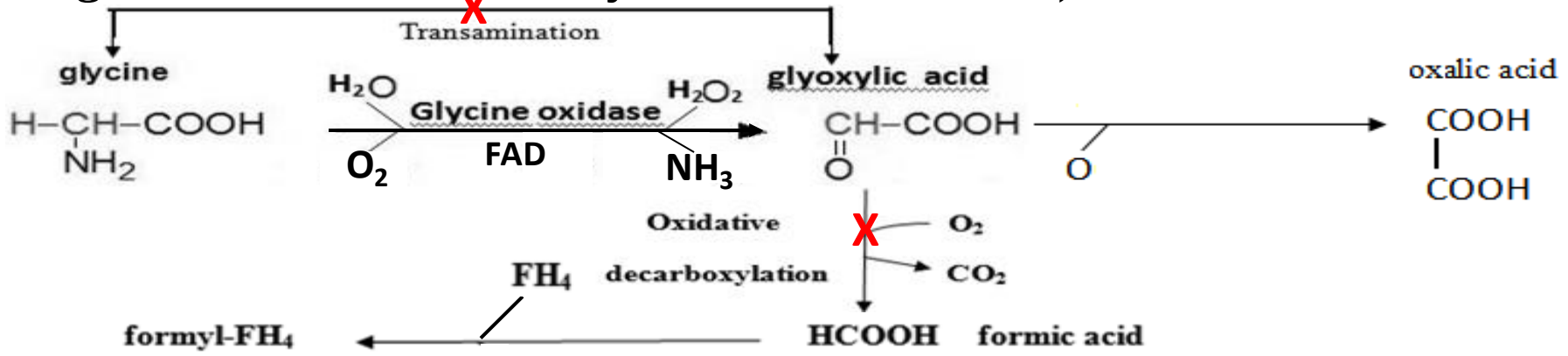
2023

Inborn metabolic errors of glycine

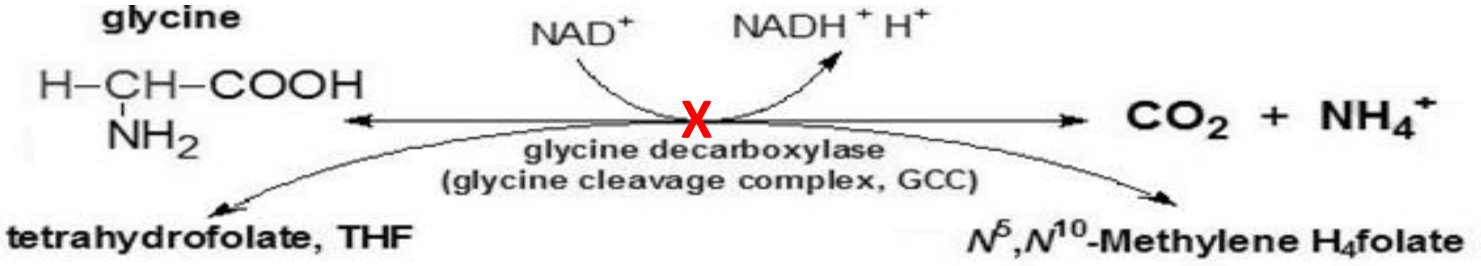
A. Primary hyperoxaluria: congenital ↓ metabolism of **glyoxalic** acid by: **oxidative decarboxylation** to formic acid, or **transamination** to glycine

*Glyoxalic acid is accumulated and is oxidized to oxalic acid.

↑ oxalate in urine → **insoluble** calcium oxalate stone in urinary tract (Large stones if bilateral may cause renal failure)



B. Hyperglycinemia: defective glycine **cleavage** system



C. Glycinuria: congenital ↓ renal tubular **reabsorption** of glycine.

Inborn errors of cysteine & cystine metabolism

A. Cystinuria (cystine-lysinuria or diaminoaciduria):

Autosomal recessive (AR) genetic defect in renal tubular **reabsorption** of **cystine, ornithine, lysine & arginine** → ↑ amounts of the 4 amino acids **in urine**

- Being water insoluble, cystine precipitates → **cystine stones.**
- **Treatment:** increasing urine volume, alkalanization of urine which increase solubility of cystine and giving D-Penicillamine.

B. Cystinosis (cystine storage disease): Autosomal recessive (AR)

- **Genetic** disease characterized by **deposition** of cystine crystals in **many tissues** especially reticuloendothelial cells.
- There is **impaired renal function** & **generalized aminoaciduria**.
- It is fatal and infants usually die at early age from renal failure.

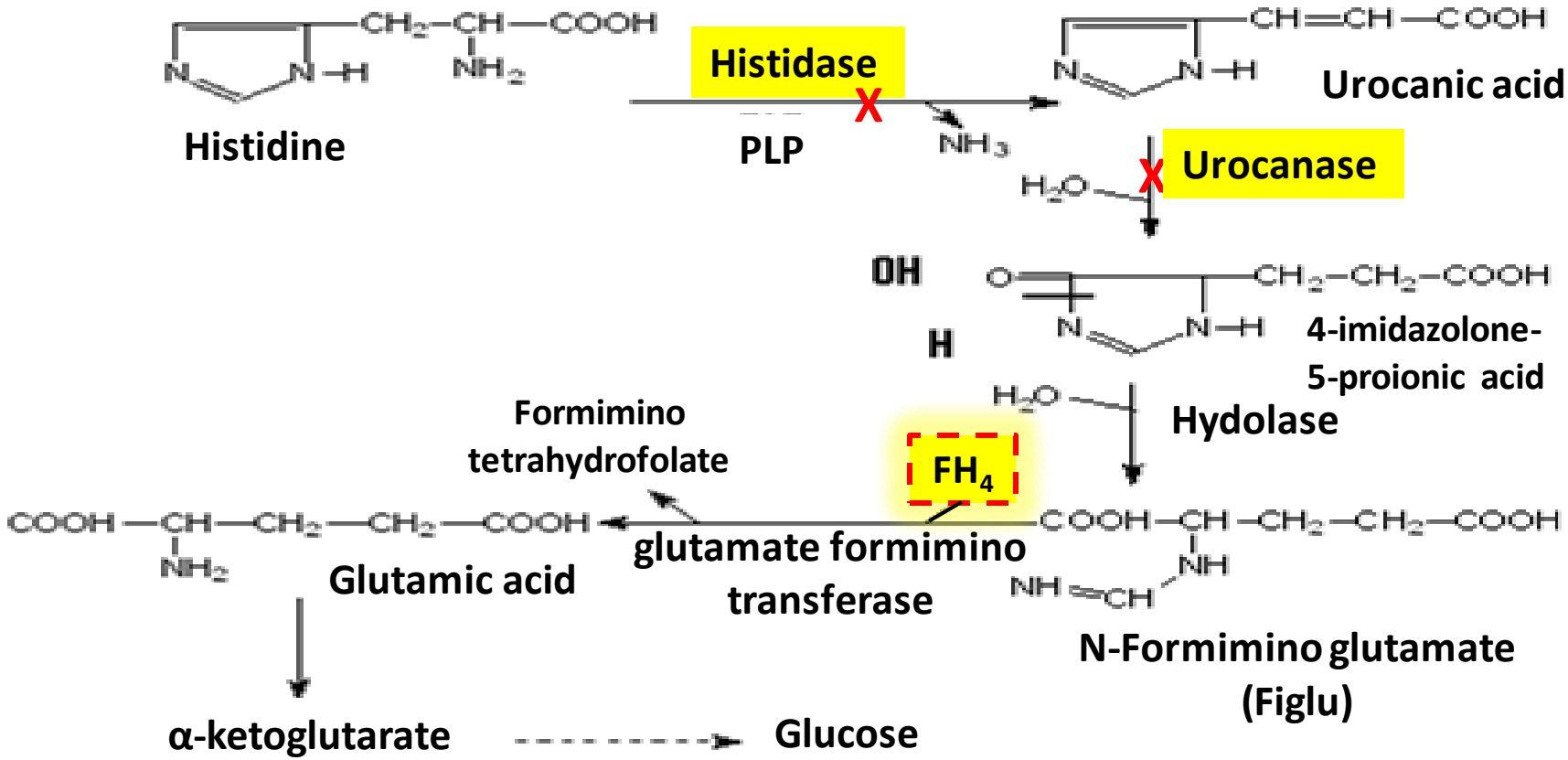
Metabolic errors of histidine metabolism

A. Histidinemia: defective histidase → ↑ blood & urinary histidine

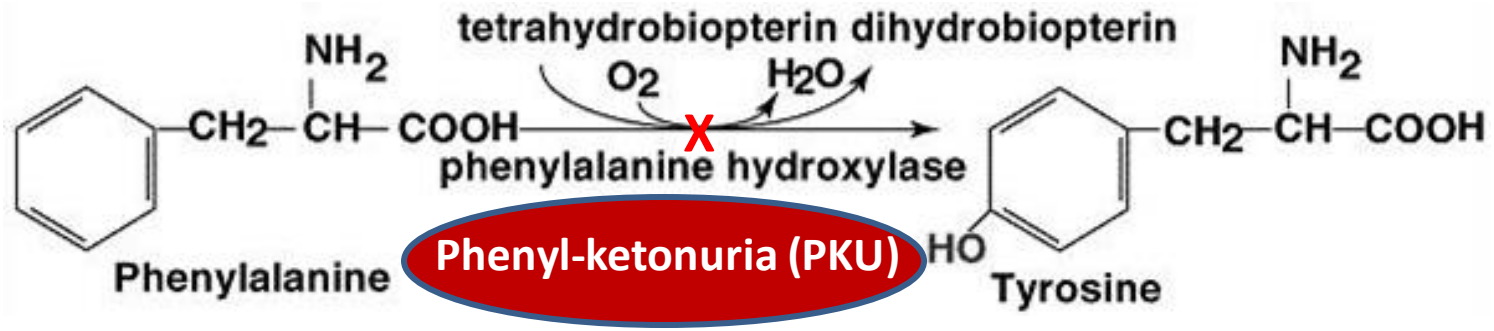
- it is characterized by delayed speech.

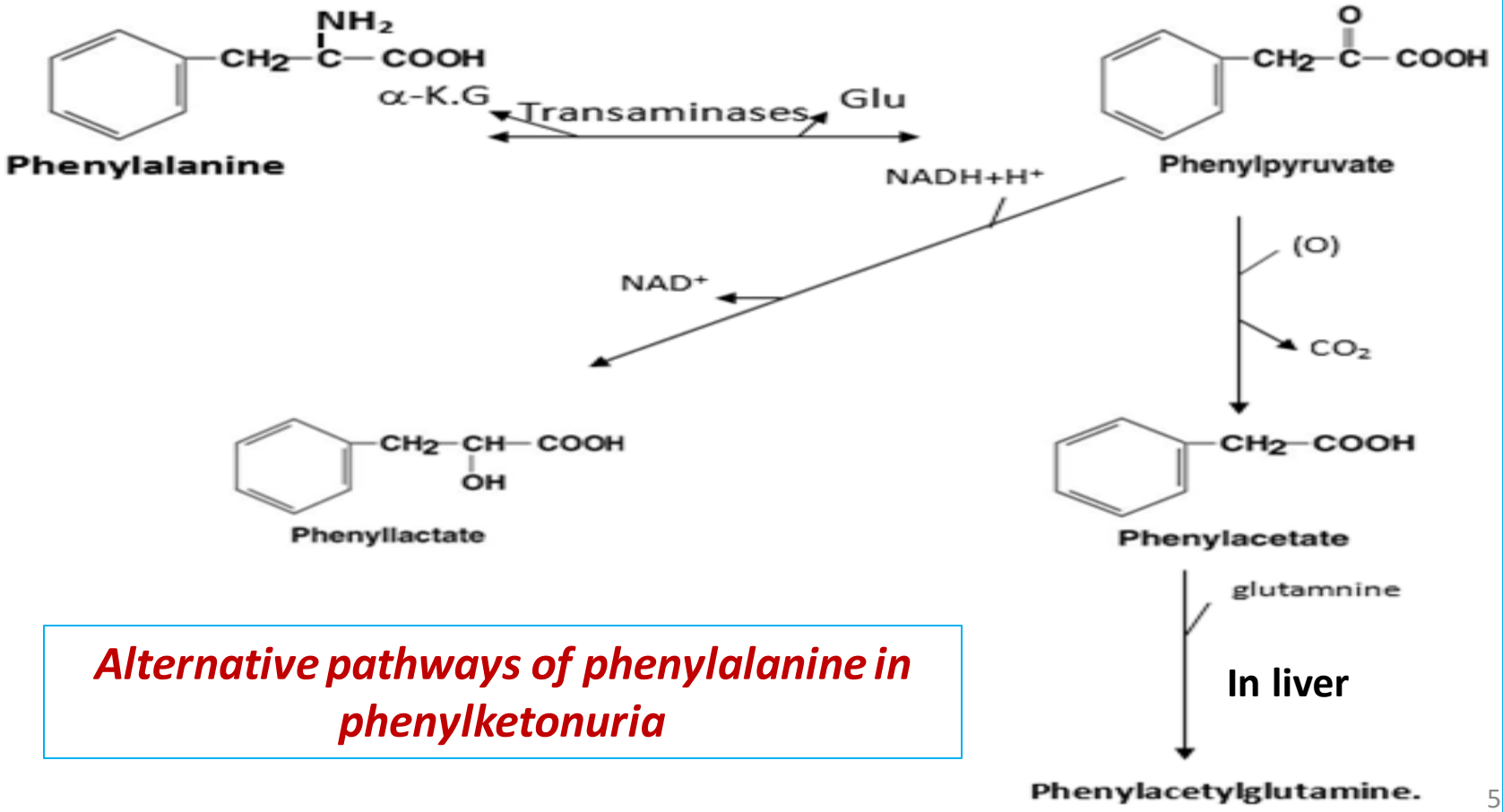
B. Urocanic aciduria: defective urocanase → ↑ urocanate in urine (the only symptom)

C. Folic acid deficiency: ↑ formimino glutamic acid **(figlu)** → excreted in urine (a diagnostic test after giving big dose of histidine)



Inborn errors of phenylalanine & tyrosine





Alternative pathways of phenylalanine in phenylketonuria

Inborn errors of phenylalanine & tyrosine

A. Phenyl-ketonuria (PKU):

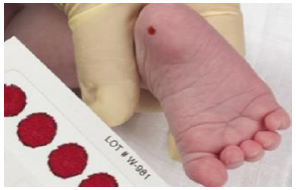
***Inheritence:** autosomal recessive

***Causes:** 1. deficiency of phenylalanine hydroxylase (classic PKU)

2. deficiency of tetrahydrobiopterin (BH4) (1-2% of cases)

↑ phenylalanine & its metabolites (phenylpyruvate, phenylacetate, phenyllactate & phenylacetylglutamine) in tissues, blood & urine (musty)

***Clinically:** Mental retardation by the age of one year & hypopigmentation of skin, hair & iris



***Diagnosis:** 1. Neonatal screening for hyperphenylalaninmia

2. blood test for ↑ phenylalanine & its metabolites (in the 1st 24 -48 hours of life)

3. BH4 loading test: normalize phenylalanine in BH4 deficiency

***Treatment:** must be started early in the first days (1st week) of life by giving diet very low phenyl alanine & rich in tyrosine (Tyrosine becomes essential). BH4 supplementation may be given in rare cases.

Case 1:

A-2-week-old infant with refusal to feed, lethargy, excessive cry and irritability, responded positively to a test for phenylketonuria. Serum Phenylalanine was 30 mg/dl and Tyrosine was 2mg/dl. A diagnosis of classical phenylketonuria (PKU) was made.

What products normally produced from tyrosine in the body?

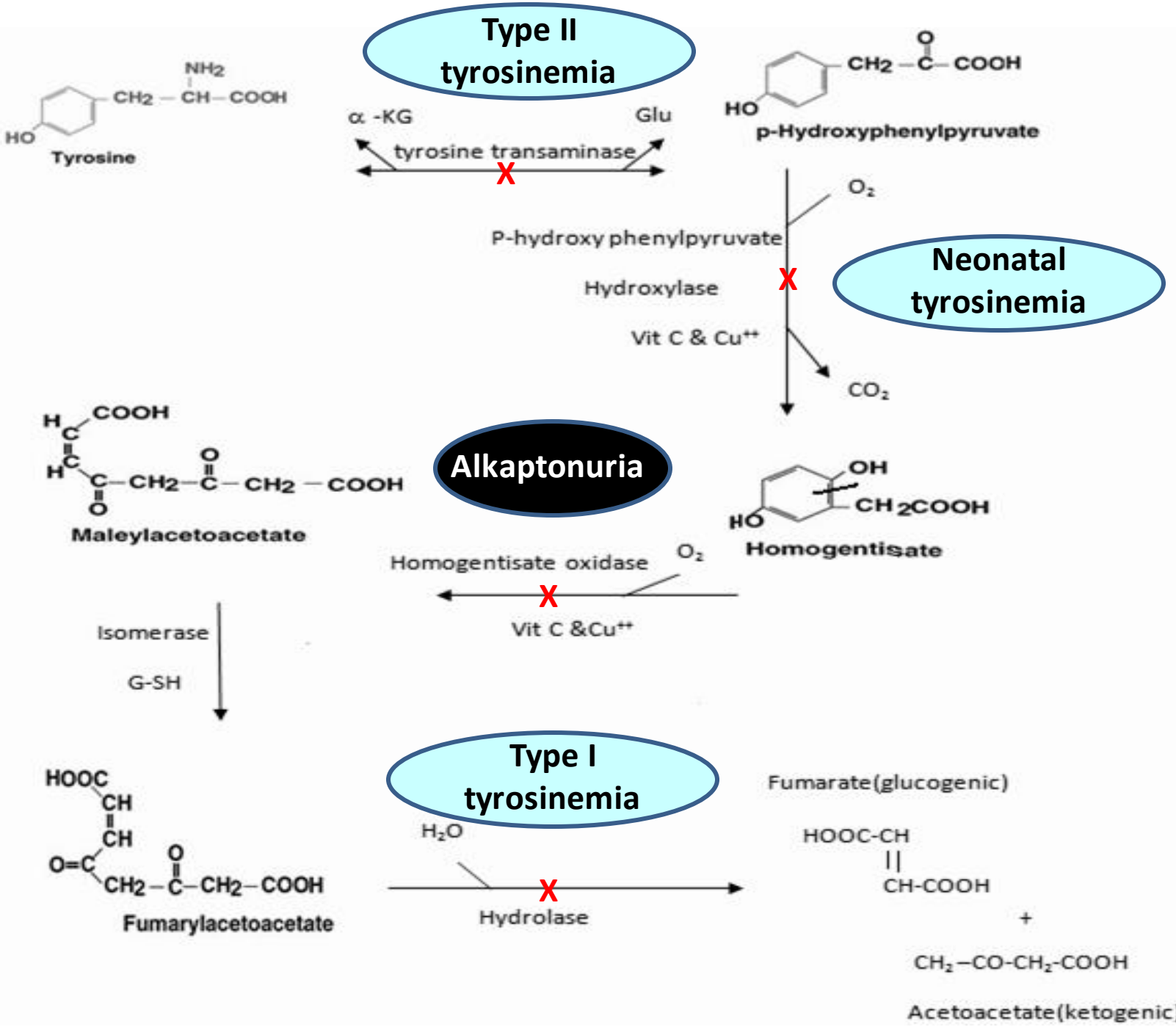
What is the defective enzyme in PKU?

Why it should be detected as early as possible?

(PKU has gradual course, easy diagnosis & monitoring of the disease so mental retardation can be prevented)

What is the treatment for this disease?

N.B. A normal blood phenylalanine level is about 1 mg/dl.
In classic PKU, levels are usually greater than 20 mg/dl.


Type II tyrosinemia
Tyrosine
α -KG
Glu
tyrosine transaminase
p-Hydroxyphenylpyruvate
O2
P-hydroxy phenylpyruvate
Hydroxylase
Vit C & Cu++
CO2
Neonatal tyrosinemia
Maleylacetoacetate
Alkaptonuria
Homogentisate
Homogentisate oxidase
O2
Vit C &Cu++
Isomerase
G-SH
Type I tyrosinemia
Fumarylacetoacetate
H2O
Hydrolase
Fumarate(glucogenic)
Acetoacetate(ketogenic)

Inborn errors of phenylalanine & tyrosine

B. Tyrosinemia:

***Inheritence:** autosomal recessive

***Causes:**

Types of Tyrosinemia	Enzyme defects
- Type I (Tyrosinosis)	- Fumaryl acetoacetate hydrolyase
- Type II	- Tyrosine transaminase
- Neonatal tyrosinemia	- P-hydroxyphenylpyruvate hydroxylase

***Clinically:** Failure to thrive and most cases die at early ages from liver failure

***Diagnosis:** all types have high levels of plasma tyrosine

***Treatment:** The main line of treatment is to give diet low in tyrosine and phenylalanine.

Inborn errors of phenylalanine & tyrosine

C. Alkaptonuria:

***Inheritence:** autosomal recessive

***Causes:** deficiency of homogentisate oxidase →

homogentisic acid accumulates in tissues, blood & urine

***Clinically:** **black urine, ochronosis & arthritis**

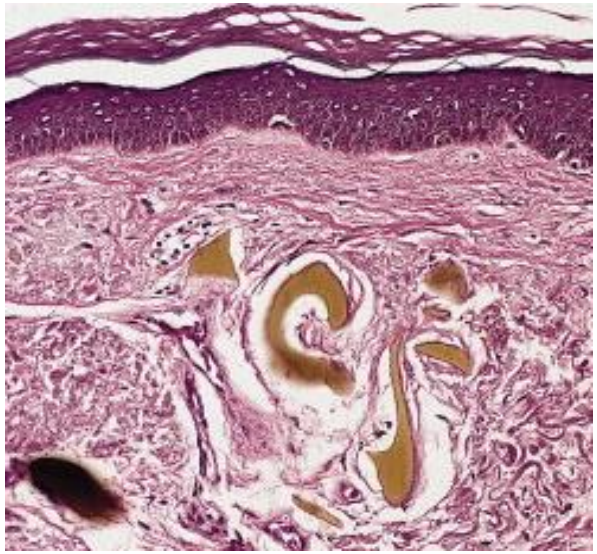
- On exposure to air, urine becomes black as homogentisic acid is oxidized to brownish **black** pigments called alkapton.
- Deposition in connective tissues → generalized pigmentation of connective tissues **(ochronosis)**.
- **Arthritis** when homogentisic acid is deposited in cartilage.

***Diagnosis:** ↑ homogentisic acid in tissues, blood & urine

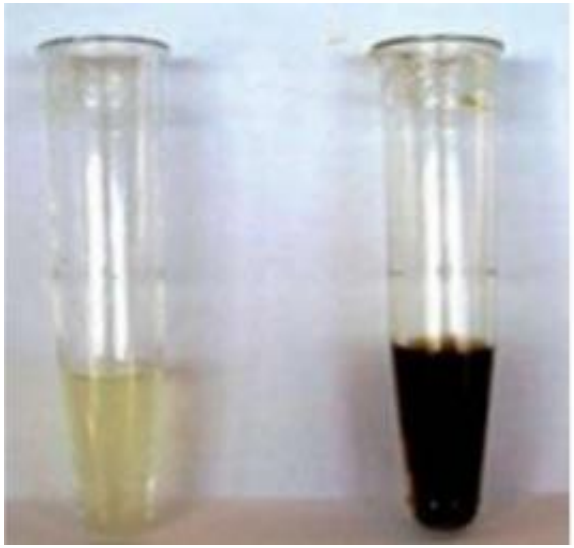
(urine: +ve Fehling test due to reducing power of homogentisate)

***Treatment:** No cure, treatment aims to ameliorate symptoms.

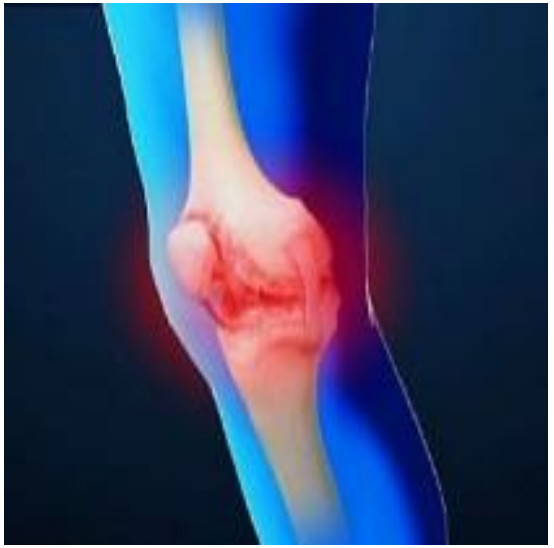
Reduce phenylalanine & tyrosine intake. Vitamin C may be supplied



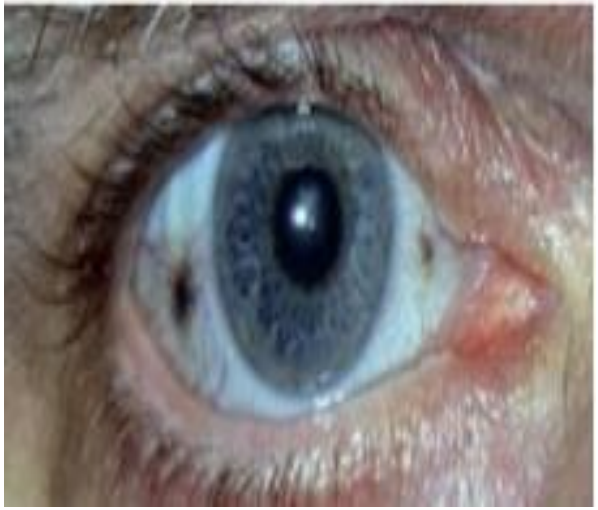
Homogentisate precipitates in tissue

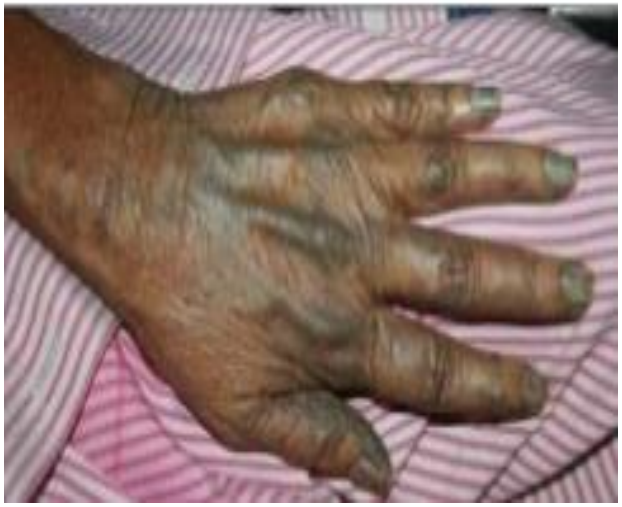


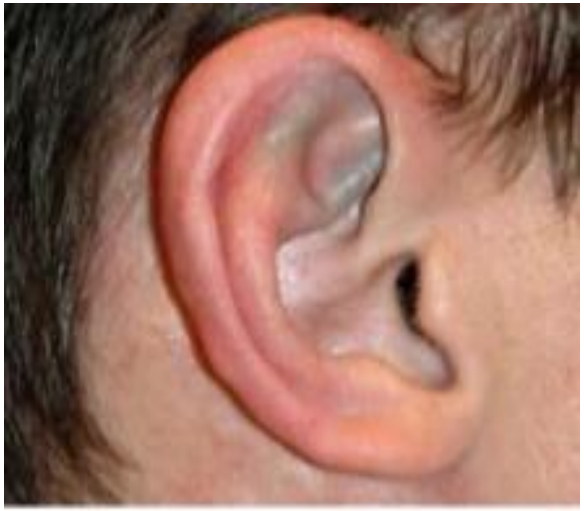
Fresh voided & long-standing urine



Arthritis







Pigmentation of tissues (sclera, hand & ear)

Case 2

A two week – old child was brought to the emergency. His parents were fearful of being poisoned as they noted black discoloration on the diaper. They had delayed disposing one of the child's diapers. Later, they realized that all the diapers turned black when kept for a longer time. The pediatrician examined the child and explained that their sibling might have an amino acid disorder.

- **What is the possible cause of this disorder?**
- **What is the cause of blackening of the diapers?**
- **How can this defect be treated?**

Inborn errors of phenylalanine & tyrosine

D. Albinism:

***Inheritence:** autosomal recessive

***Causes:** deficiency of tyrosinase (copper dependent enzyme)

***Clinically:** failure melanin formation in skin, hair & iris.

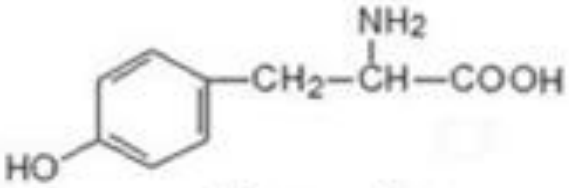
1- White hair

2- Photophopia and Refractive errors

3- Sensitive skin to UV rays → burns → cancer

***Diagnosis:** based on appearance of skin, hair, & eyes.

***Treatment:** is to relieve symptoms & protect skin & eyes



Tyrosine

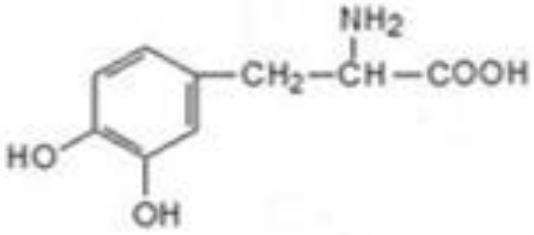
NADPH+H+ NADP+

BH4 & Cu++

X

Tyrosinase

O2 (hydroxylase activity) H2O



DOPA

N.B

BH4 is needed in hydroxylation of phenylalanine, tyrosine & tryptophan

Cu++

2H X

Tyrosinase

(DOPA oxidase activity)

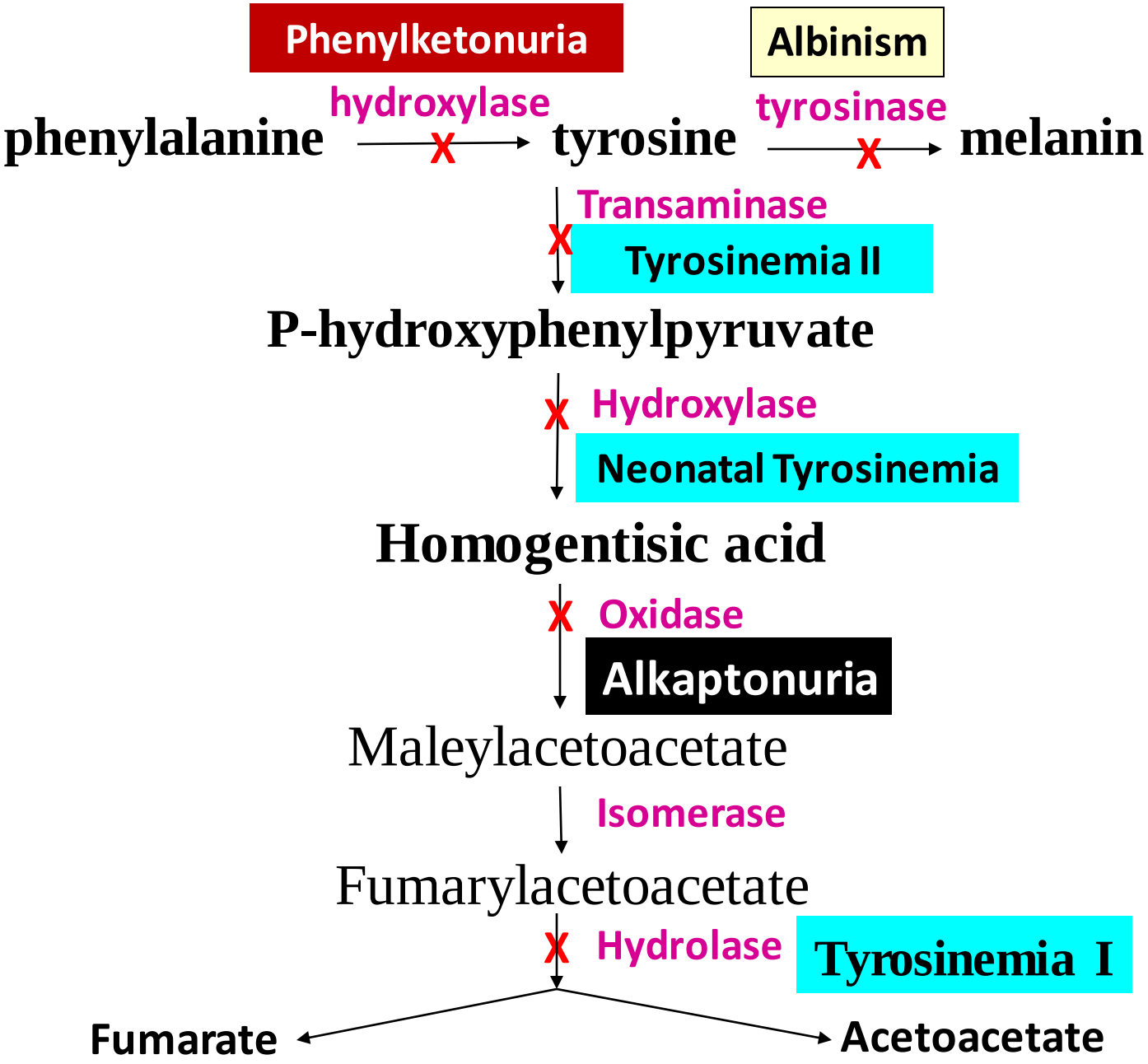
Dopa quinone

Case 3

A-2-month – old baby girl was brought by her parents for consultation. She had pale skin, blonde hair and pink iris. The baby girl was otherwise healthy, feeding well but was unable to fix the gaze. Parents revealed that their first two children, a boy and a girl, had complete albinism, but the parents themselves were normal. The eye examination of the child showed absence of pigment in the iris & retina. A diagnosis of albinism was made for the child.

- **What is the defect in Albinism?**
- **What is the pattern of inheritance?**
- **How can this disease be treated?**

Inborn errors of phenylalanine & tyrosine



Metabolic errors of tryptophan

A. Hartnup:

***Inheritence:** autosomal recessive

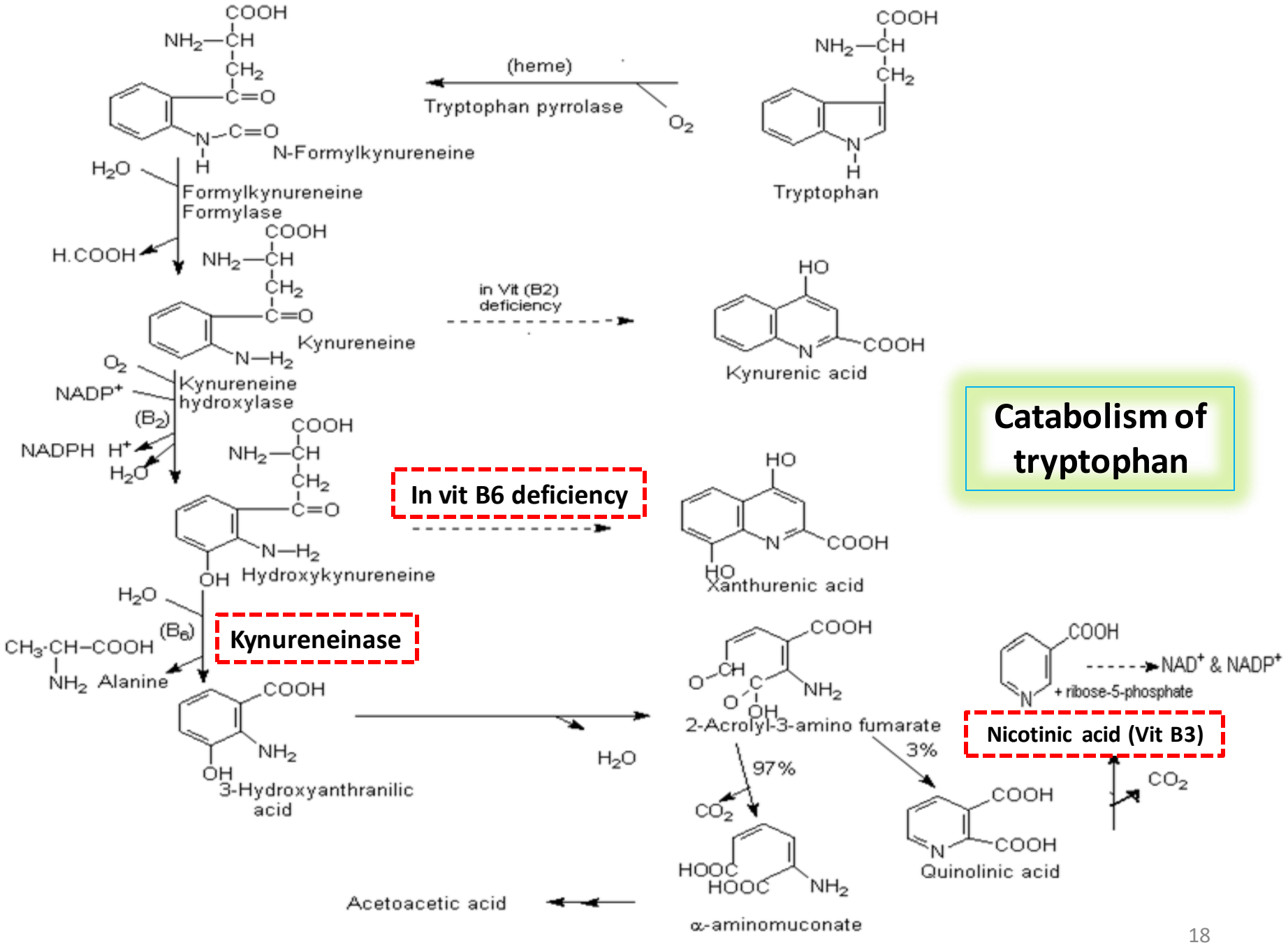
***Causes:** hereditary defect of intestinal absorption & renal tubular reabsorption for neutral amino acids particularly tryptophan (gene mutation in sodium-dependent neutral amino acid transporter). Tryptophan passes in stools or undergoes putrefaction into indole and skatole.

***Clinically:** failure to thrive, pellagra like skin rash (nicotinic acid or vit B3 deficiency), cerebellar ataxia & mental retardation

***Diagnosis:** ↑ Neutral amino acids, tryptophan & tryptophan degradation products as indole acetate in urine

***Treatment:** high–protein diet, supply vit B3 if deficient & avoid excessive exposure to sunlight by protective clothes

B. Vitamin B6 deficiency: →↑ increases excretion of xanthurenic acid in urine due to inhibition of kynureninase


(heme)
Tryptophan pyrrolase
O_2
N-Formylkynureneine
Tryptophan
H_2O
Formylkynureneine Formylase
H.COOH
Kynureneine
in Vit (B2) deficiency
Kynurenic acid
O_2
$NADP^+$
Kynureneine hydroxylase
(B_2)
NADPH H^+
H_2O
Hydroxykynureneine
In vit B6 deficiency
Xanthurenic acid
H_2O
(B_6)
Kynureneinase
Alanine
3-Hydroxyanthranilic acid
H_2O
2-Acrolyl-3-amino fumarate
97%
3%
CO_2
NAD^+ & $NADP^+$
+ ribose-5-phosphate
Nicotinic acid (Vit B3)
CO_2
Quinolinic acid
Acetoacetic acid
α-aminomuconate
Catabolism of tryptophan

Case 4

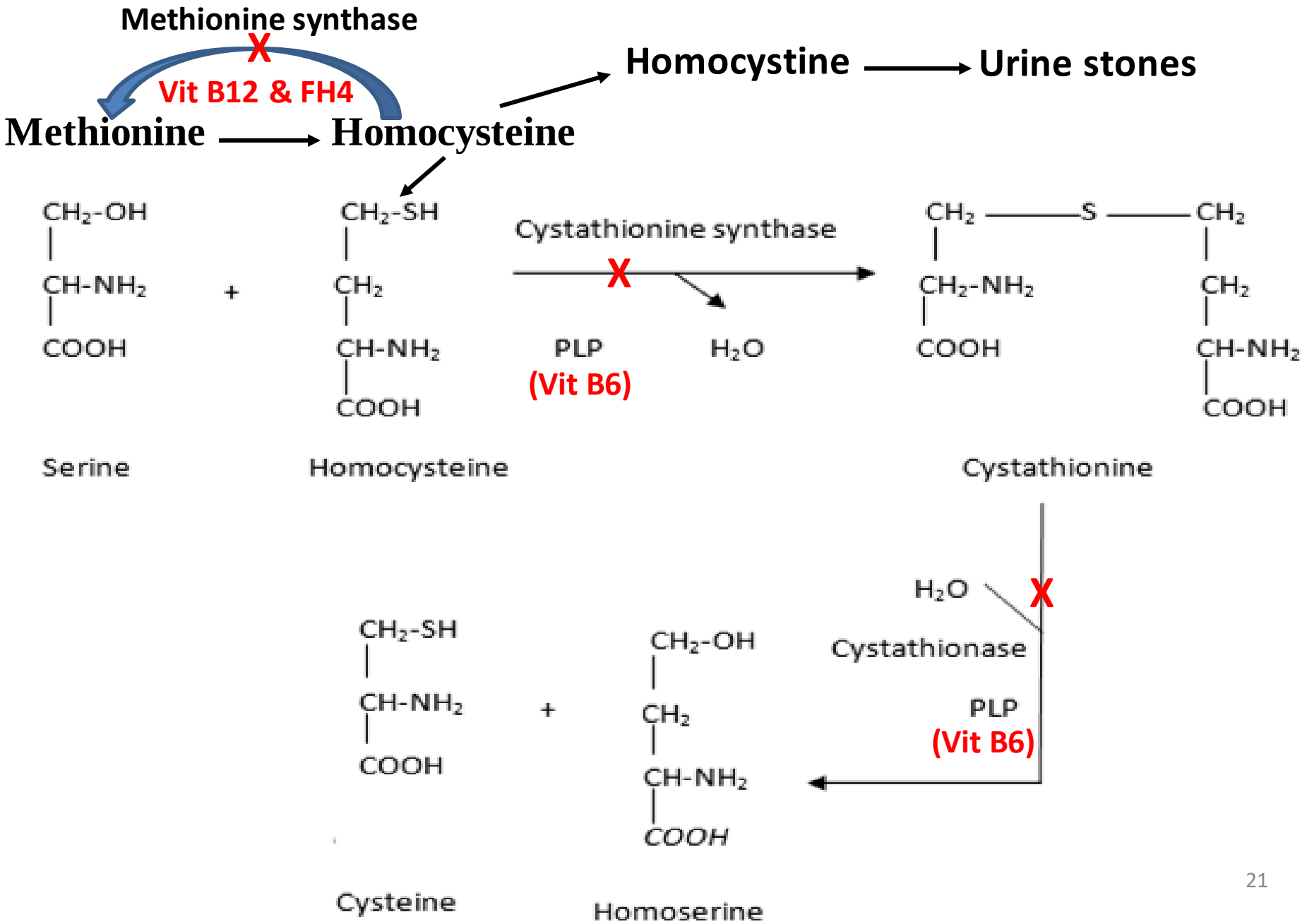
A 12 – year – old boy presented with a red scaly rash & mild cerebellar ataxia. His mother thought that the boy is suffering from pellagra because the same symptoms in her older daughter had been diagnosed earlier. Large amounts of free amino acids were found in his urine. When the older daughter had a recurrent attack of ataxia and her urine contained excessive amount of amino acids. Two other siblings had also aminoaciduria; however four others were normal. The parents were asymptomatic, but a family history revealed that they were first cousins.

What abnormality could account for this condition?

What is the relation of this condition to the skin rashes?

- **How can this defect be treated?**

Metabolic errors of methionine & homocysteine



Metabolic errors of methionine & homocysteine

A. Homocystinuria:

***Inheritence:** autosomal recessive (AR)

***Causes:**

- **Type I:** deficiency of cystathionine synthase (or PLP) characterized by high level of plasma methionine and excretion of large amounts of homocystine and SAM in urine. Cysteine becomes essential.
- **Other types**: methionine synthase defect (or vit B12 & folate defect) → inability to remethylate homocysteine to methionine

***Clinically:** vascular thrombosis, osteoporosis, dislocation of eye lens and mental retardation.

***Diagnosis:** ↑ methionine, ↑ homocystine, ↓ cystine in body fluids

***Treatment:** diet low in methionine, rich in cysteine
also rich in vit B6, B12 & folate
intake of choline as methyl donor.

Clinical effects of Homocystinuria:

A. Increased homocysteine interacts with lysyl residue of collagen → inhibition of formation of cross linking of collagen → weak extracellular matrix:

1. Bone deformity and fracture.

2. Occular deformity & dislocation of eye lense

3. Dilatation of blood vessel wall → rupture & hemorrhage

4. Mental retardation.

B. Increased homocysteine → thiolactone (free radical) which thiolate apoprotein of LDL → aggregation of LDL that become endocytosed by macrophage which migrate under basement membrane of the vascular endothelium so it increases the risk of ischemic heart disease, atherosclerosis and thrombosis at young age.

Case 5

A six year old boy was brought to the pediatric department. He had mental and physical retardation, knock knee, arched feet and dislocated lens. Routine blood and urine examinations were within normal limits. Urine was positive for ninhydrin test. The patient was treated for 2 weeks with high doses of pyridoxin, when urine abnormality was reversed.

- **What is your provisional diagnosis?**
- **Which enzyme is defective in this patient?**
- **What is the coenzyme required for this enzyme?**

B. Cystathioninuria:

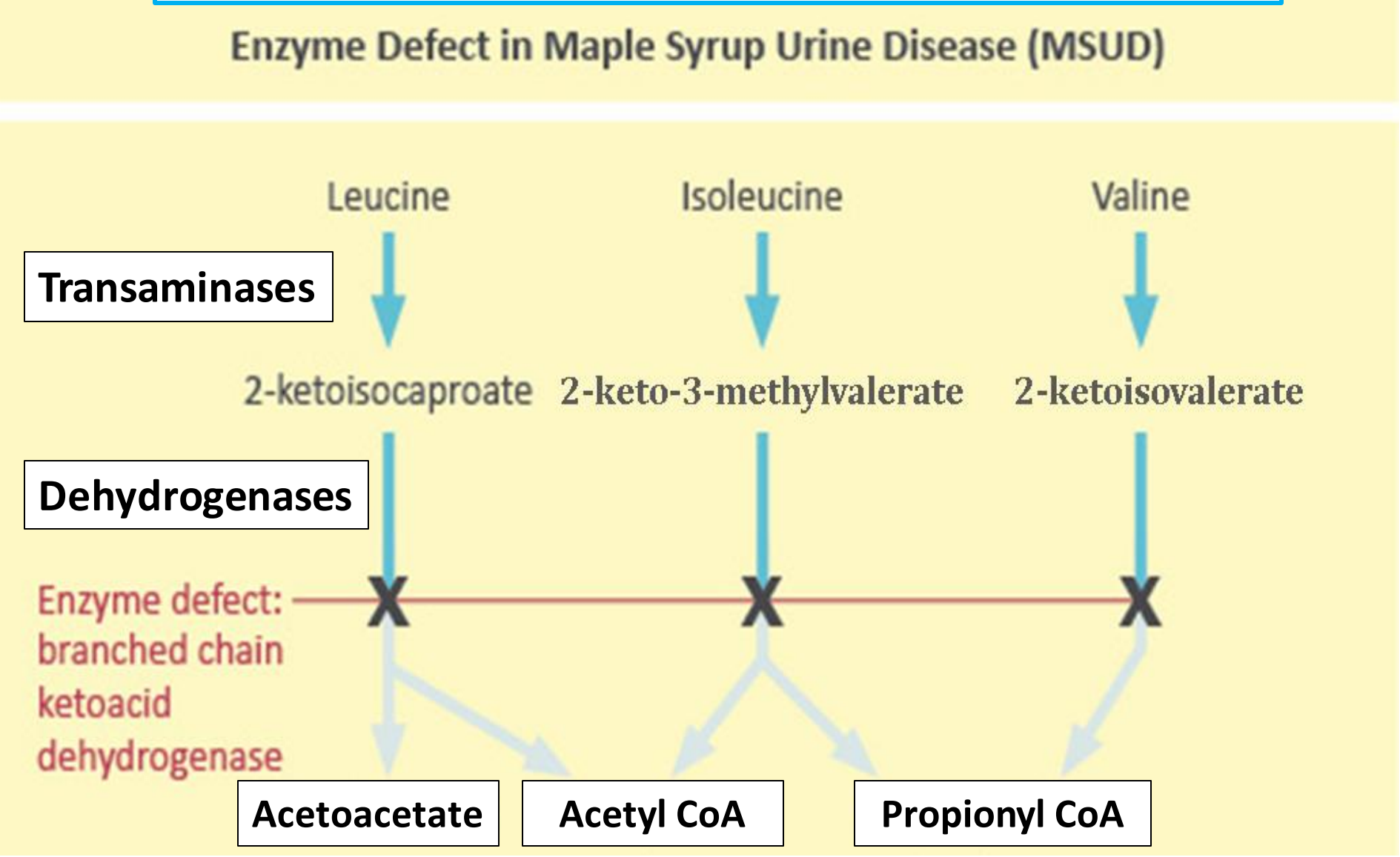
***Inheritence:** autosomal recessive

***Causes:** deficiency of cystathioninase (PLP dependent)

***Diagnosis:** excretion of large amounts of cystathionine in urine

***Treatment:** diet low in methionine, rich in cysteine, vit. B12 & B6

Metabolic errors of branched chain amino acids



Metabolic errors of branched chain amino acids

A. Maple syrup urine disease (branched – chain Keto aciduria):

***Inheritence:** autosomal recessive

***Causes:** defective branched chain α –keto acid dehydrogenase

***Clinically:** mental retardation & eventually die.

***Diagnosis:** The corresponding branched chain α –keto acids levels ↑ in plasma & urine → characteristic maple syrup odor (burnt sugar odor)

***Treatment:** A diet with minimal levels of leucine, isoleucine, and valine must be maintained to prevent neurological damage.

A careful monitoring of blood chemistry & frequent testing.

Case 6

A child presented with severe vomiting, dehydration & fever. The child was born normal but was not growing well in the last few months. There was progressive mental retardation. Urine analysis revealed the presence of branched chain amino acids and their corresponding Keto acids in high amount. Preliminary results from blood amino acid screen showed two elevated amino acids with nonpolar side chains. Blood studies showed acidosis with a low bicarbonate level. His urine had a smell of burnt sugar.

What is the probable defect?

What is the basis for these symptoms?

Case 6

Explanations:

- **Fever suggests metabolic imbalance was worsened by infection.**
- **Blood and urine in this disease have elevated levels of branched amino acids and their keto derivatives. The keto derivatives cause acidosis with low bicarbonate levels are due to depletion of alkali reserve.**
- **It is a type of organic acidemia.**
- **The condition gets its name from the distinctive burnt sugar odor of infants' urine.**