Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

INBORN ERRORS OF AMINO ACIDS METABOLISM

"TO WIN WITHOUT RISK IS TO TRIUMPH WITHOUT GLORY"

- PIERRE CORNEILLE.

Color index:

- Important.
- Doctors notes.
- Extra explanation.

* Please check out this link to know if there are any changes or additions.

OBJECTIVES:

- Identify the amino acid degradation and synthesis of non-essential amino acids.
- Recognize the metabolic defects in amino acid metabolism that lead to genetic diseases.

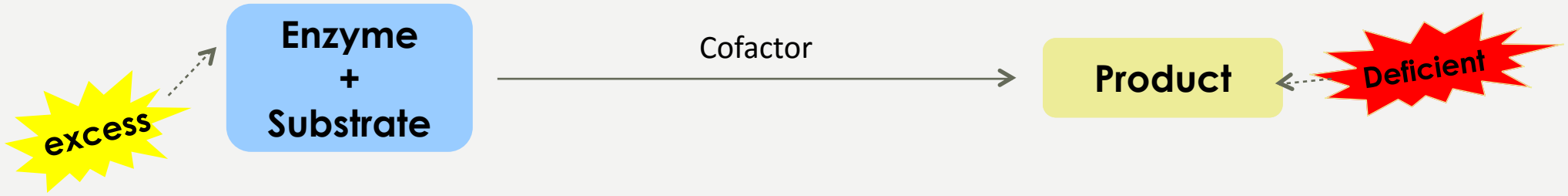
Inborn errors of amino acids metabolism

Introduction:

Amino acid metabolism is part of the whole body nitrogen metabolism. Nitrogen enters the body as amino acids in proteins and leaves the body as urea, ammonia etc. All 20 amino acids present in proteins are required for health. 12 out of the 20 amino acids can be synthesized by the body and the rest are supplied by diet. Errors in the amino acid metabolism can result in irreversible brain damage and early mortality.

❖ **They're caused by:**

Enzyme loss or deficiency (formed but not functioning) due to gene loss or gene mutation.



فكرة هذه المحاضرة مختصرة بهذي المعادلة...

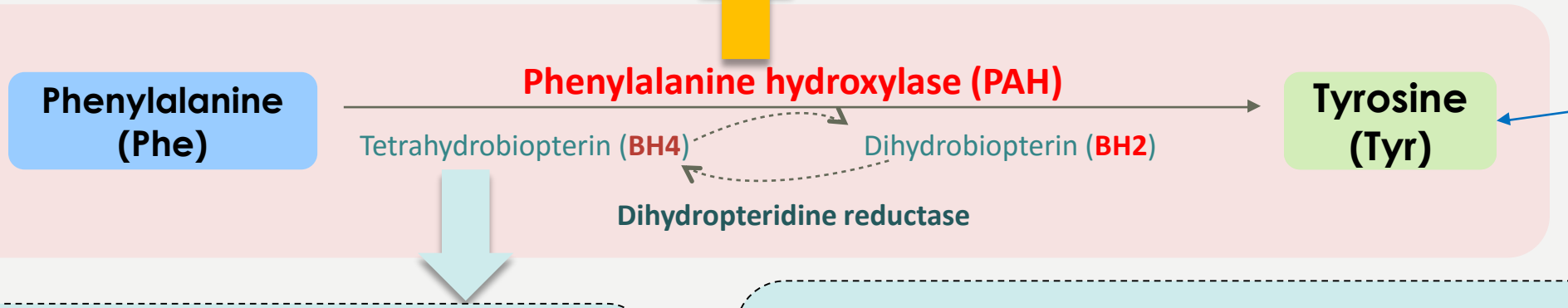
- الإنزيم في الحالة الطبيعية يقوم بتحويل السبستراين إلى ناتج ، والناتج يحتاجه جسمنا لأداء غرض معين .. قد يكون صبغة ، نيوروترانسمتر ... الخ.
- عندما يولد الشخص ومعه طفره جينيه لإحدى الجينيات المسئولة عن تكوين إنزيم ، الإنزيم لن يكون قادر على أداء وظيفته (تحويل السبستراين إلى ناتج) وعليه ستكون نسبة السبستراين في الجسم عالية، والناتج لن يكون متواجد .

Phenylketonuria (PKU):

- **most common inborn error of amino acid metabolism.**
- **What is it?** accumulation of phenylalanine, which results in hyperphenylalanemia and Deficiency of tyrosine
- **Caused By:** Deficiency of **Phenylalanine hydroxylase**.
- **Results in:** hyper-phenylalanemia and Deficiency of tyrosine.

PKU

Deficiency of Phenylalanine hydroxylase will cause classic PKU



In normal situations, Tyrosine is a non-essential amino acid "can be synthesized in the body".
Here, tyrosine becomes essential (body cannot produce it).

- Conversion of Phe to Tyr requires BH4 (Tetrahydrobioptrein) .
Even if the PAH level is normal, it won't function without BH4.
- Hence Phe is accumulated.

Deficiency of BH4 (Tetrahydrobioptrein), Caused by deficiency of:

1- Dihydropteridine reductase.
2- Dihydropteridine synthase.
3- Carbinolamine dehydratase.

Deficiency in one of them will lead to deficiency of BH4

will cause Atypical PKU "problem in BH4 recycle"

PAH requires BH4 as a coenzyme, therefore deficiencies in the cofactor will lead to hyperphenylalanemia and tyr deficiency .

the absence of BH4 in PKU leads to:

1-Phenylalanine (phe) will not be converted to Tyrosine

- There will be an Elevated phe conc. in tissues, plasma and urine. Normally Phenylalanine is degraded to phenyllactate, phenylacetate, and phenylpyruvate. So when there's a high conc. of phe, there will be a high conc. of these three, and thus they will be excreted in urine causing **the mousy odor** (smell) of urine.

2-Tyrosine will not be converted to catecholamines

3-Tryptophan will not be converted to serotonin

- Tyrosine is involved in the synthesis of melanin.
(melanin is pigment of the skin which gives the skin its color).
So no or less tyrosine → no or less melanin.
So what if the patient has a deficiency in melanin?
He/she will have hypopigmentation.
Hypopigmentation:
-it is a deficiency in melanin. (in this case this deficiency is due to the deficiency of tyrosine).
- It has the same symptoms as albinism (white hair, white skin, vision defect).
- Hydroxylation of tyrosine by tyrosinase is inhibited by high phenylalanine conc.

the absence of BH4 in PKU leads to:

❖ **What is catecholamine?** It's a group of amino acids that contain catechol (benzene ring bound to 2 hydroxyl groups), this group include: epinephrine, norepinephrine and dopamine.

1-Phenylalanine (phe) will not be converted to Tyrosine

2-Tyrosine will not be converted to catecholamines

- BH4 is a cofactor for the enzyme tyrosine hydroxylase, which is the first step to produce catecholamines, thus if it was defect the synthesis of this group will be inhibited.

REMEMBER:
المشكلة هنا مو في نقص التايروسين ، بل في نقص الانزيم الي يحوله لهذي المجموعة من الامينو اسيدز.

Catecholamines and serotonin are neurotransmitters

3-Tryptophan will not be converted to serotonin

- Tryptophan is an essential amino acid (we take it from the food).
- BH4 is a cofactor for the enzyme tryptophan hydroxylase, thus if it was defect, the synthesis of serotonin will be inhibited.
- Serotonin main function : involving in intestine motility.

Phenylketonuria (PKU):

Symptoms

CNS

- Mental retardation
- failure to walk or talk
- seizures
- microcephaly

By the age of 1 year, so we have to restrict the phe within the first weeks of life

the defference between seziures and convulation:
seizures happen in CNS ,can happen for a long time.
while convulation can happen to muscles, and it is temporary.

Hypo-pigmination

- fair hair
- light skin colour
- blue eyes

ليه ما قلنا ان الميلانين اختفى كليًا؟
لأننا نحصل عليه من الطعام، فمازال عندنا كمية منه+
ممكن أن يتكون بطرق أخرى .

Treatment

Life long **phe-restricted diet + tyrosine supplementation**

Diagnosis:

Prenatal diagnosis

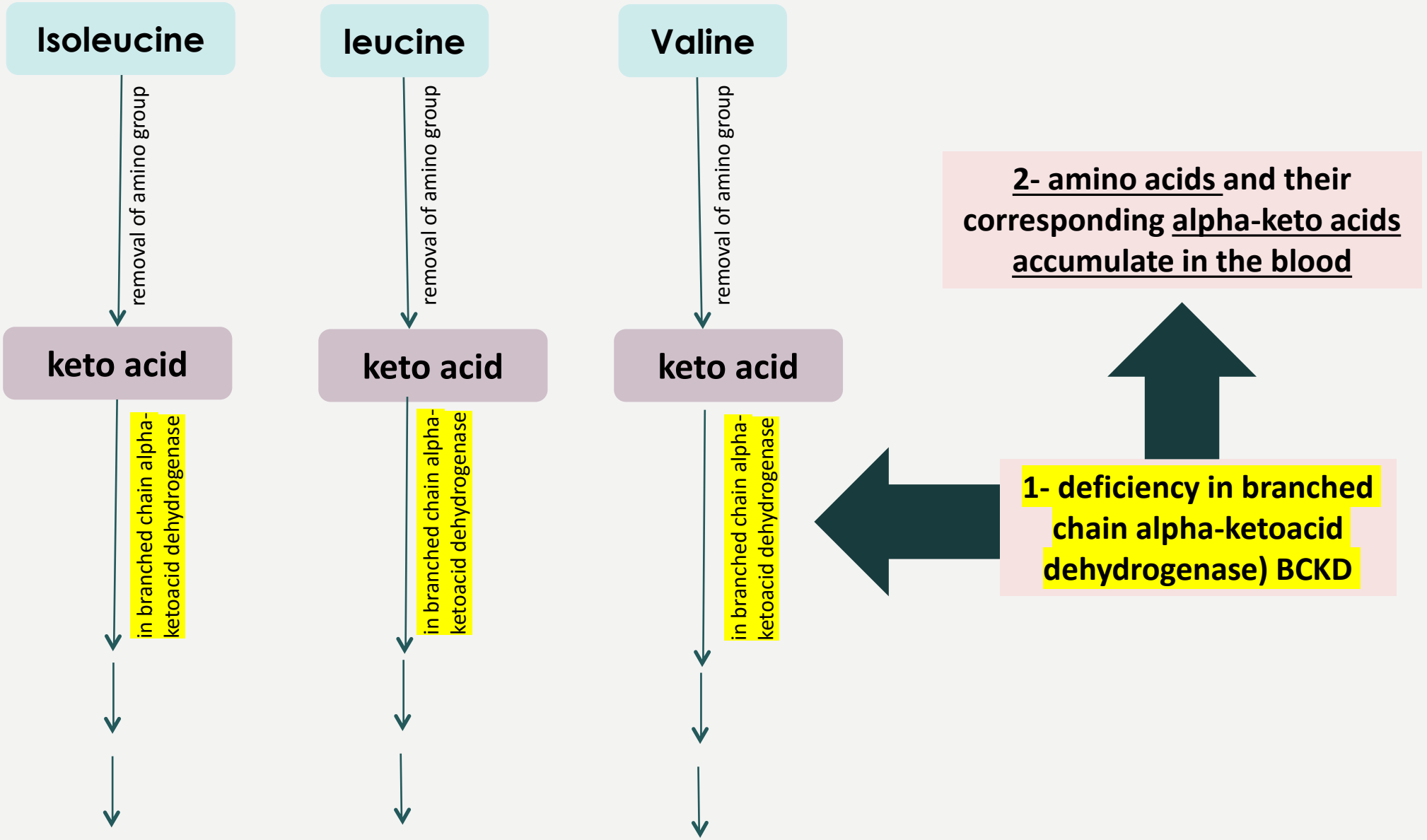
It is done by detecting gene mutation in fetus

Neonatal diagnosis

in infants is done by measuring blood phe levels

We must wait 24- 48 hours before measuring phe after birth, because the maternal enzymes usually clear the phe build up, and during this period the baby will be drinking milk and phe will have the time to accumulate to a measurable level.

Maple Syrup urine disease



Maple Syrup urine disease

- **What is it?** It is an autosomal recessive disorder in which there's a partial or complete **deficiency in branched chain alpha-ketoacid dehydrogenase) BCKD**, an enzyme that **decarboxylateates** **leucine**, **isoleucine**, and **valine**.
- **These** Branched **amino acids and their corresponding alpha-keto acids** **accumulate in the blood** causing a toxic effect that interferes with the brain functions.
- **Characteristic: maple syrup odor** (smell) **of urine.**
- **Treatment:** Limeted intake of leucine, isoleuocine and valine causes no toxic effects.

We limit the intake of these three by causing malabsorption or blockage so the body can't use them.

Symptoms

- Mental retardation.
- Physical disability.
- Metabolic acidosis.
  (to be specific: Ketoacidosis due to accumulation of ketone acids).

TYPES

Classic type

- Most common type of MSUD.
- Little or no BCKD activity

Intermediate and intermittent forms

- Milder symptoms.
- Higher levels of enzyme activity (up to 30% of normal).

There is a mutation, but not in the active site of the enzyme, that's why it has a mild activity.

Thiamin-responsive form

- Respond to high doses of thiamin, which will increase BCKD activities.

النوع الثالث هو الثاني لكن نفع معه الثيامين، لكن ما راح ينفع مع الكلاسيك لو تعطيه "خيشة" ثيامين ☺

Albinism

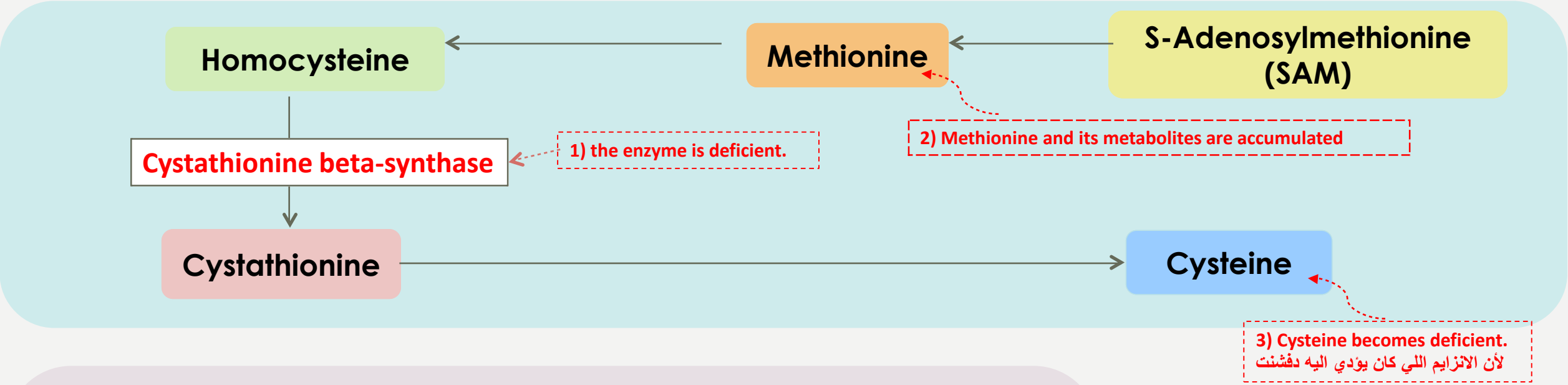
❖ **What is it?** A group of conditions in which ***a <u>defect in tyrosine metabolism</u>*** (due to **tyrosinase deficiency**) results in a deficiency in the production of **<u>melanin</u>**.

المشكلة هنا في الانزيم وليست في التايروسين نفسه.
يعني حتى لو عطيناه تايروسين ما راح يفيده .

THESE DEFECTS RESULTS IN:

- **Absence of melanin pigment**
- **White hair and skin**
- **Vision defects and photophobia** (sunlight hurts their eyes).

Homocystinuria



❖ **How does Homocystinuria occur?**

It occurs due to defects in homocysteine metabolism

❖ **What is the deficient enzyme in this error?**

cystathionine β-synthase Which Converts: **homocysteine to cystathione**

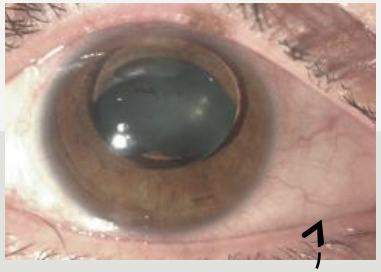
❖ **What is the consequence of cystathionine b-synthase deficiency?**

High plasma and urine levels of homocysteine methionine and low levels of cysteine

What is homocysteine?

It's methionine (amino acid) got converted to homocysteine during methionine degradation.

Homocystinuria



❖ What are the risk factors accompanying this phenomena?

High plasma homocysteine is a risk factor for **atherosclerosis** and heart disease
It also results in : Skeletal abnormalities (long limbs and fingers), osteoporosis, mental retardation, **displacement of eye lens**

Treatment of Homocystinuria

- Oral administration of **vitamins B6**, B12 and **folate** → Vitamin B6 is a cofactor for cystathionine b-synthase
- Methionine-restricted diet

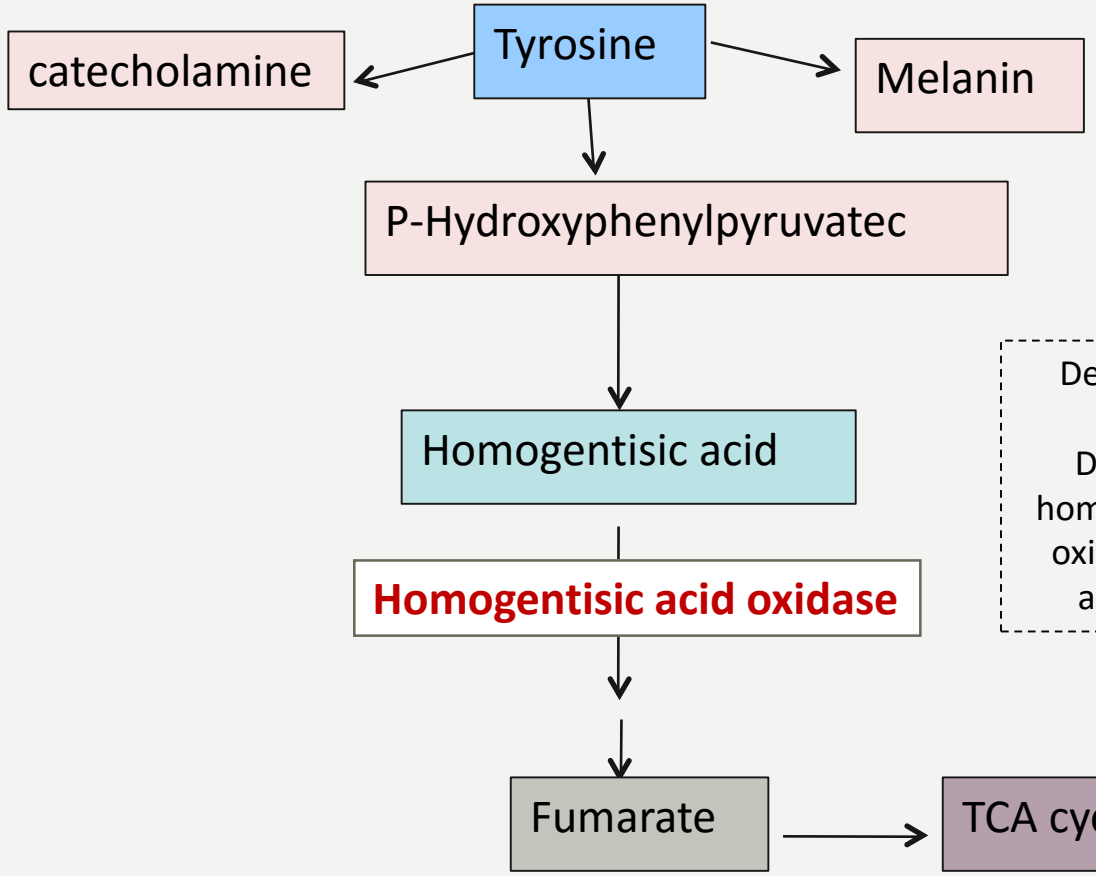
HYPERHOMOCYSTEINEMIA IS ALSO ASSOCIATED WITH:

- Neural tube defect (spina bifida)
- Vascular disease (atherosclerosis)
- Heart disease

Homocyteinuria

Alkaptonuria

- **What is Alkaptonuria?**
  A rare disease of tyrosine degradation
- **the deficient enzyme: homogentisic acid oxidase**
- **What is the consequence of homogentisic acid oxidase deficiency?**
  Homogentisic acid is accumulated in tissue and cartilage
- **What is Homogentisic aciduria?**
  Homogentisic aciduria: elevated homogentisic acid in urine



Degradation of tyrosine
Deficiency of homogentisic acid oxidase leads to alkaptonuria

Note: Alkaptonuria is a mild form of a disease, but after the age of 40 the symptoms become worsen

Alkaptonuria

Alkaptonuria

What happens if Homogentisic acid got accumulated?	Homogentisic acid is oxidized to dark pigment in urine over time
What are the consequances?	Arthritis, black pigmentation of cartilage and tissue
Clincal course?	Usually asymptomatic until adulthood
Treatment?	Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation

Note: Homogentisic acid is a dark pigment and a product from tyrosine degradation (the infants will only have dark urine and once they get older, the dark pigments will start showing on the cartilages).

The physical sign in this condition is not the odor, but the color of the urine.

MCQs

1. When phenyllactate, phenylacetate, and phenylpyruvate got excreted in urine, they will cause :

A. maple syrup odor.
B. black color.
C. mousy odor.
D. non of above.

2. Which one of the following is a neurotransmitter?

A. Tyrosine
B. Tryptophan
C. Phenylalanine
D. Serotonine

3. Which one of the following is a symptom of PKU?

A. Physical disability .
B. Seizures .
C. Black pigmentation.
D. Heart disease.

4. In hypopigmentation, which statement of the following is not true:

A. It can occur due to the absence of BH4.
B. It occurs due to a deficiency of tyrosinase.
C. The tyrosine is defect.
D. Usually associated with some CNS symptoms.

5 homocysteinuria is due to defect in.

A. Cystathionine b-synthase.
B. Tyrosine.
C. BH4.

6. Vitamin ……. Is a cofactor of:

A. B12.
B. B6.
C. B1.
D. D3.

1-C
2-D
3-B
4-B
5-A
6-C

MCQs

7. Alkaptouria is characterized by:

A. Black pigmentation of cartilage.
B. black color.
C. Skeletal abnormalities .
D. Mental retardation.

8. All of the following can cause Atypical PKU, except:

A. Dihydropteridine reductase deficiency .
B. Dihydropteridine synthase deficiency
C. Carbinolamine dehydratase deficiency
D. Phenylalanine hydroxylase deficiency

9. Albinism is caused by a Deficiency of :

A. Phenylalanine hydroxylase.
B. tyrosinase
C. Cystathionine beta-synthase
D. Dihydropteridine reductase

10. Hyperhomocysteinemia

A. spina bifida
B. atherosclerosis
C. Heart diseases
D. All of the above.

11. In Maple Syrup urine disease, Branched amino acids and their corresponding alpha-keto acids accumulate in the blood

A. T
B. F

7-A
8-D
9-B
10-D
11-A

SAQs

❖ **A newborn has been screened for a positive for a defect in phenylalanine hydroxylase enzyme.**

- What is your diagnosis?

PKU

- How you will treat him?

restriction of dietary phenylalanine

- What dietary supplementation you will give him? And why?

Tyrosine. Tyrosine is normally produced from metabolism of phenylalanine

- If left untreated what could happen?

It may progress to mental retardation,sezuires and light skin.

❖ **A 3-year-old boy is seen in clinic. He was apparently normal at birth, but later developed failure to thrive and developmental delay. He has fair skin and blue eyes. He also has a history of cataracts. His older brother had a myocardial infarction at the age of 18. Laboratory testing of his urine showed an increase in the level of an amino acid.**

- What is the amino acid?

Homocysteine

- What is the most likely mechanism responsible for the pathology?

cystathionine b-synthase deficiency Which Converts: homocysteine to cystathione

- What vitamine deficiency mimics his disorder?

Vit B6

- How you will treat him?

Oral administration of vitamins B6, B12 and folate.
Methioninerestricted diet

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- خوله العريني .
- ريفان هاشم .
- غاده القصيمي.
- منيره الحسيني .
- نوف الرشيد .

- خالد النعيم .
- ثاني معافا .
- فارس المطيري .
- محمد الصهيل .
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