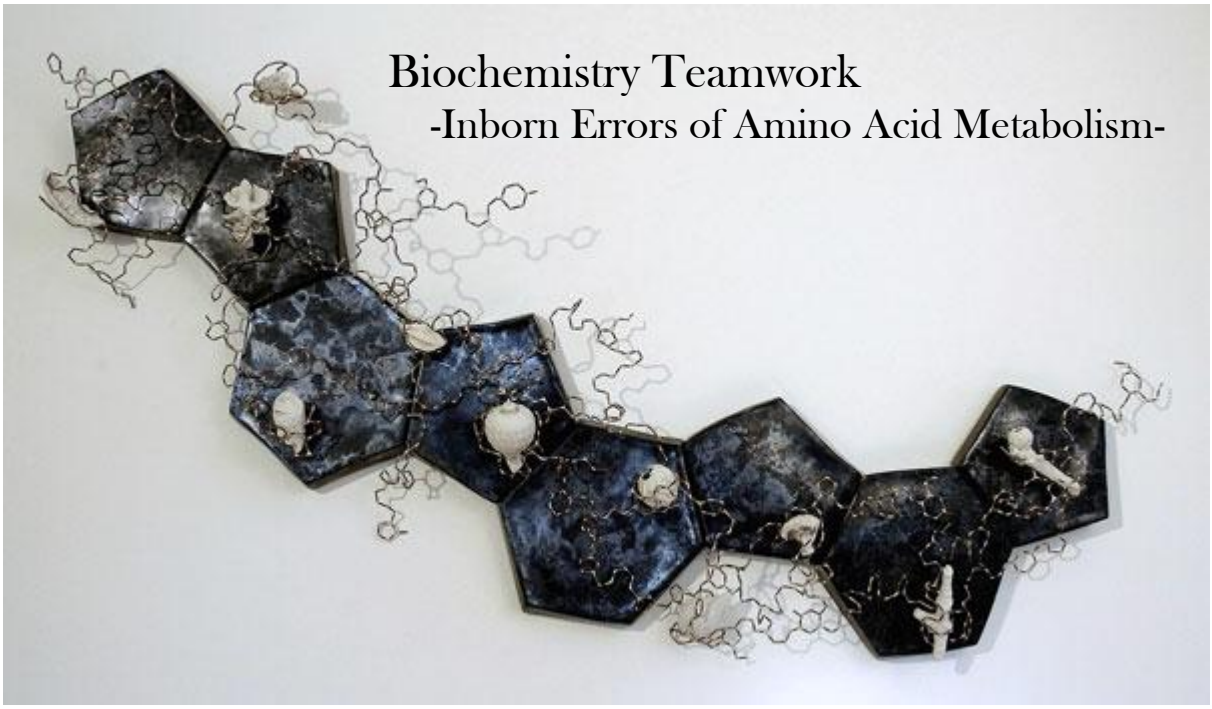

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Inborn Errors of Amino Acid Metabolism

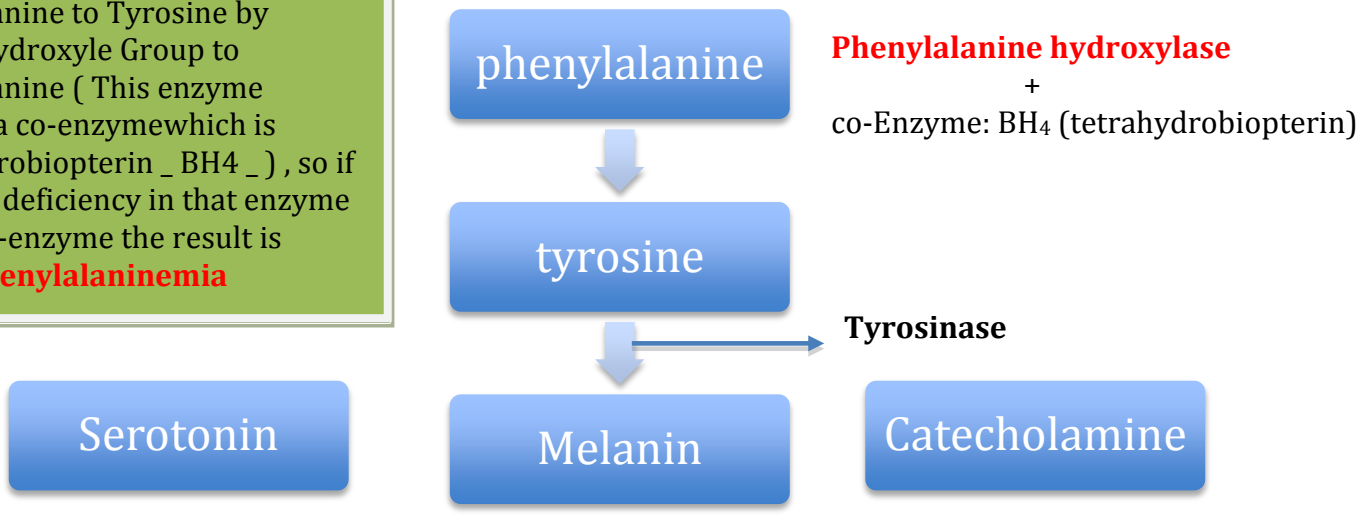
➔genetic mistake of gene loss or mutation leading to a disease
it is an abnormal protein synthesis leading to 1. **Enzyme deficiency**
2. **Co-Enzyme deficiency**

➔this leads to accumulation of substrates and lack of products.

PKU: phenylketonuria

Phenylalanine hydroxylase is an enzyme which converts Phenylalanine to Tyrosine by adding Hydroxyle Group to Phenylalanine (This enzyme requires a co-enzymewhich is Tetrahydrobiopterin _ BH4 _) , so if there is a deficiency in that enzyme OR it's co-enzyme the result is **Hyperphenylalaninemia**

it's the **most common** AA disorder



1.The Classical (Primary) Type PKU:

The defect is in the enzyme **phynylalaninehydroxylase** resulting in an accumulation of phenylanine➔phenylketones in the urine and hyperphenylalaninemia

Main Enzyme that converts BH2 to BH4

2. The Atypical (Secondary)Type PKU:

the defect is in the recycling of the co-factor: **BH_4**; when it is used up it is transformed into BH_2.
BH_2 is later converted to BH_4 via 3 enzymes: 1.Dihydropteridine reductase
2.Dihydrobiopterin synthetase
3.Carbinolamine dehydratase

A defect in Dihydropteridine reductase results in the atypical PKU (Secondary cause)(NOTE : both Dihydrobiopterin Synthetase and Carbinolamine Dehydratase bring or synthesis BH2 to Dihydropterine Reductase to convert it to BH4 , so if there is a defect in ONE of These TWO enzyme (2,3) there will be BH2 that is brought to the main enzyme (1) but LESS than normal > raise in Phenylalanine Concentration . But if there is a defect in Both Enzymes (2,3) there will be no BH2 > as a result No BH4) , **even if phenylalanine hydroxylase level is normal.** ➔no conversion to tyrosine

- when tyrosine is not formed all other products will be deficient:

Only in case of BH4 deficiency, has nothing to do with Tyrosine deficiency

← Serotonin (neurotransmitter)➔ CNS abnormality
1. Catecholamine (neurotransmitter)➔ CNS abnormality
2.**Melanin** (skin pigment) ➔hypo-pigmentation (fair skin – White in color)

When this pathway is inhibited and the non-essential amino acid tyrosine is low, the body compensates by using the dietary source of tyrosine (essential); however, the accumulated Phenylalanine inhibits the enzyme **tyrosinase**

This enzyme is responsible for the initial step in melanin formation from tyrosine.

Elevated phenylalanine in the plasma, tissues and urine.
It is degraded to phenyllactate, phenylacetate, and Phenylpyruvate which give the urine **a mousy odor**.

Clinical Manifestations:

CNS symptoms: Mental retardation, failure to walk or talk, seizures, etc.
Hypopigmentation due to: Deficiency of melanin
Hydroxylation of tyrosine by tyrosinase is inhibited by high phe conc.

The management is too hard in case of Neonatal and they usually die

Diagnosis:

Prenatal by detecting gene mutation in fetus

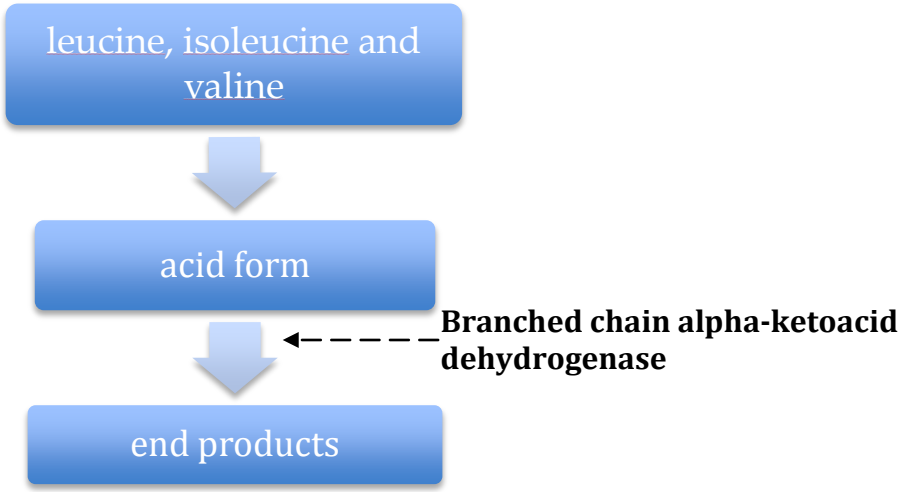
Neonatal diagnosis in infants is done by measuring blood phe levels

Treatment:

Life long phe-restricted diet: decreased protein intake along with protein supplements with limited phenylalanine content. Increased fruit and cereal intake.

Maple Syrup Urine Disease:

Maple syrup odor of urine



Defect in **alpha-ketoacid dehydrogenase** will result in the accumulation of both the original and the acidic forms of them.

Types:

Classic type: Most common, due to very little or no activity of a-ketoacid dehydrogenase

Intermediate and intermittent forms: partial enzyme activity (3-15%), symptoms are milder

Thiamin-responsive form: High doses of thiamin (Vitamin B1)increases a-ketoacid dehydrogenase activity (because Vitamin B1 is a co-Enzyme). These are a percentage of the patients who are responsive.

Symptoms: mental retardation, physical disability, metabolic acidosis (due to vomiting and dehydration associated with this disease)

Treatment:

Limited intake of leucine, isoleucine and valine

Albinism:

As mentioned above

Melanin biosynthesis:

Tyrosine —**tyrosinase**→ melanin (a pigment of hair, skin and eyes)

Defected **tyrosinase** ➔ absent melanin ➔ albino patient

Hair and skin appear white

Defected vision, photophobia

*high risk of skin cancer

Homocystinuria:

defects in homocysteine metabolism:

Homocysteine —**Cystathionine b-synthase**→ Cystathione

Deficiency of **cystathionine b-synthase**

High plasma and urine levels of homocysteine and methionine

Homocysteine is a risk factor for atherosclerosis and heart disease

- Skeletal abnormalities, osteoporosis, mental retardation, displacement of eye lens "ectopialensis"
- Neural tube defect (spina bifida) This result from ➔
- Vascular disease (atherosclerosis)
- Heart disease

Deficiency of:
•Tetrahydrofolate
•Methioninesynthase
•Vitamin B_6, B_{12}
•**Folic acid**

Treatment:
Oral administration of vitamins B_6,B_{12} and folate
Vitamin B_6 is a cofactor for cystathionine b-synthase
Methionine-restricted diet

Alkaptonuria

A rare disease of tyrosine degradation
Due to deficiency of **homogentisic acid oxidase**
This enzyme is required during the late stages of tyrosine degradation pathway

Homogentisic acid is accumulated in tissue and cartilage➔arthritis
Homogentisicaciduria: elevated homogentisic acid in urine➔ oxidized to dark urine over time
And black pigmentation of cartlidge
This is usually asymptomatic until adulthood with arthritis as the main complaint.

Treatment:
Restricted intake of tyrosine and phenylalanine to reducehomogentisic acid and dark pigmentation

IMPORTANT SUMMARY

	Disease	Enzyme	Aminoacids involved
1	Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine
2	Maple syrup urine disease	α-ketoacid dehydrogenase	Isoleucine, leucine and valine
3	Albinism	Tyrosinase	Tyrosine
4	Homocystinuria	Cystathionine β-synthase	Methionine
5	Alkaptonuria	Homogentisic acid oxidase	Tyrosine and phenylalanine

Dr Othman said that you should know at least the enzyme that is deficient and in which disease ☺

***Summary table done by Hadeel Al-subaie

	Phenylketonuria (PKU)	Maple Syrup Urine Disease (MSUD)	Albinism	Homocyteinuria	Alkaptonuria
Deficient enzyme	**Classic:** phenylalanine hydroxylase **Atypical:** BH4	a-ketoacid dehydrogenase	tyrosinase	cystathionine b-synthase	homogentisic acid oxidase
Accumulated	phenylalanine	leucine, isoleucine and valine	tyrosine	homocysteine and methionine	Homogentisic acid
	No tyrosine, melanin		No melanin		Tyrosine is present
Sign & symptoms	1-Mental retardation. 2- failure to walk or talk. 3- Seizures. 4- Hypopigmentation (Light skin) 5- mousy odor urine due to Phe is degraded to phenyllactate, phenylacetate, and phenylpyruvate.	1- mental retardation. 2- physical disability. 3- metabolic acidosis.	1- Hair and skin appear white. 2- Vision defects. 3- photophobia.	1- Skeletal abnormalities. 2- osteoporosis. 3- mental retardation 4- displacement of eye lens.	1- urine is oxidized to dark pigment over time. 2- Arthritis. 3- Black pigmentation of cartilage & tissue. 4- Usually asymptomatic until adulthood
Treatment	Life long phe-restricted diet	Limited intake of leucine, isoleucine and valine	__	1- Oral administration of vitamins B6, B12 and folate. 2- Methionine-restricted diet.	Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation
Notes	Atypical is Caused by the deficiency of: 1- Dihydropteridine reductase. 2- Dihydrobiopterin synthetase. 3- Carbinolamine dehydratase.	Types: 1- Classic. 2-Intermediate forms. 3- Thiamin-	__	a risk factor for: 1- atherosclerosis. 2- heart disease 3- Neural tube defect (spina bifida)	__

QUESTIONS

1- Which one of the following enzymes is deficient in case of **Classic phenylketonuria** PKU ?
   A- Tyrosinase
   B- Dihydropteridine reductase .
   C- Phenylalanine Hydroxylase .
   D- B & C

2- Which one of the following co-enzymes is required to activate Phenylalanine hydroxylase ?
   A- Tetrahydrobiopterin (BH4)
   B- Dihydrobiopterin (BH2)
   C- Dihydropteridine reductase .
   D- Phenylalanine Synthase .

3- Which of the following is a risk factor of Homocysteinemia ?
   A- Atherosclerosis
   B- Spinal bifida
   C- Increase intake of Isoleucine
   D- A&B

4- Which one of the following statements is correct ?
   A- If there is BH4 deficiency , still the body can synthesis Serotonin .
   B- If there are Phenylalanine hydroxylase and BH4 deficiency , still the body can synthesis Serotonin.
   C- If there is a deficiency in Phenylalanine hydroxylase but BH4 is intact , still the body can synthesis Serotonin .
   D- All statements are WRONG .

5- Ali is child who has a white hair color and he cannot see very well in day time .. which one of the following enzymes is deficient in such a case ?
   A- Albinotase
   B- Homogentisic acid oxidase
   C- Tyrosinase
   D- Cystathionine B-Synthase .

Answers : C,A,D,C,C