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King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Inborn Errors of Amino Acid Metabolism

Biochemistry Team 437

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Introduction

- Inborn errors of amino acid metabolism result from a mutation in the gene responsible for making the enzyme involved in the amino acid synthesis pathway.
- There are around 50 errors known so far, but generally their incidence is very rare.
- Phenylketonuria is the most common one.
- Most of these errors are routinely tested right after birth.

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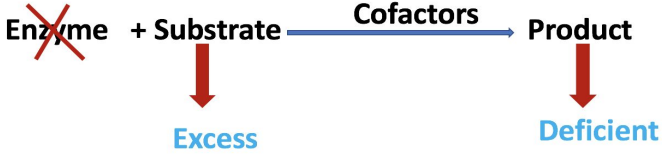
Inborn Errors of Amino Acid Metabolism

Caused by enzyme loss or deficiency due to gene mutation

If the enzyme or its cofactor is deficient, the products will be deficient and the substrate will accumulate.



- The normal function of the enzyme is converting substrates into products.
- The enzyme might or might not be helped by a cofactor.
- If the enzyme or its cofactor is deficient, the products will be deficient and the substrate will accumulate.
- The symptoms result from accumulation of the substrate.
- Generally the symptoms involve intellectual and developmental disorders.
- According to the type of mutation, the enzyme might be completely lost or just deficient.
- If the enzyme was completely lost, no products will be produced at all, and the substrates will accumulate in huge amounts, leading to a more severe disease.
- If the enzyme was not completely lost, some substrates will be converted to products and the disease will be less severe.
- Deficiency of the product is not always present, because there might be another pathway that results in the same product.

Inborn Diseases of Amino Acid Metabolism

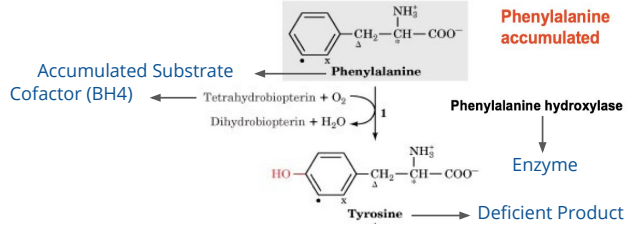
- Phenylketonuria (Most common)
- Maple Syrup Urine Disease
- Albinism
- Homocystinuria
- Alkaptonuria

IMPORTANT!!
You have to know for each disease:
1- The enzyme that is deficient
2- Substrate which is accumulated
3- The product that is deficient

Phenylketonuria (PKU)

- Most Common disease of amino acid metabolism
- Due to deficiency of Phenylalanine hydroxylase enzyme (PAH)
- Results in hyperphenylalaninemia and tyrosine deficiency
    - **Substrate:** Phenylalanine "accumulate"
    - **Enzyme:** Phenylalanine hydroxylase
    - **Cofactor:** Tetrahydrobiopterin (BH4) which is converted to dihydrobiopterin (BH2)
    - **Product:** Tyrosine "becomes deficient"

Pathway of Classical PKU



tip

You don't need to memorise structures or pathways, only memorize the substrates, enzymes, cofactors and products.

Tyrosine is normally a non-essential amino acid. but in case of enzyme deficiency, the body can't produce it so it becomes essential, therefore tyrosine supplements are given to the patient "meaning it is conditionally essential".

- Essential = can't be produced by the body
- Non essential = can be produced by the body

cont .Phenylketonuria (PKU)

Other reasons for hyperphenylalaninemia:

- Deficiency of Tetrahydrobiopterin (BH4)
  - Conversion of Phenylalanine to Tyrosine requires tetrahydrobiopterin (BH4)
  - Even if phenylalanine hydroxylase level is normal, the enzyme will not function without BH4
  - Hence Phenylalanine is accumulated

- **Atypical hyperphenylalaninemia:**

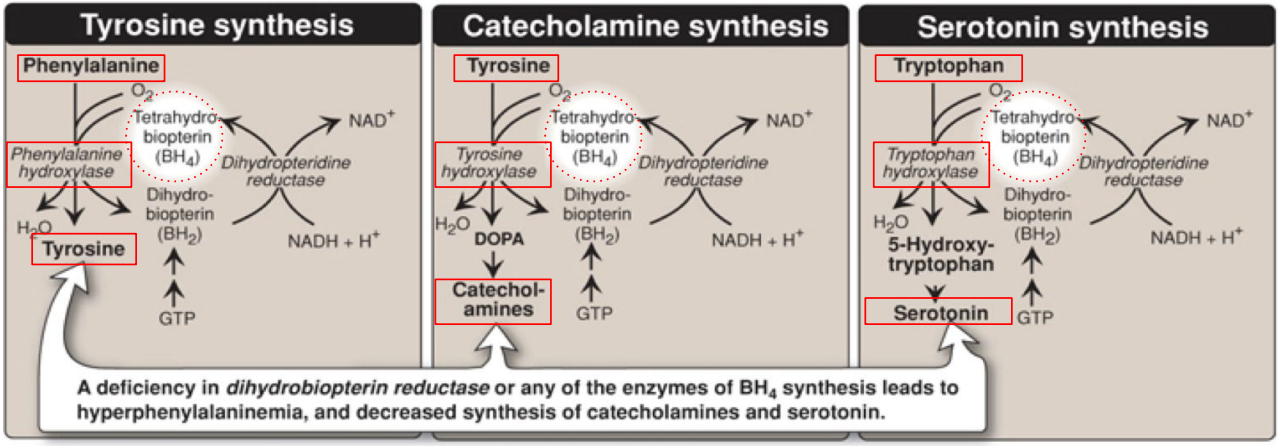
  Due to deficiency of:
  - Dihydropteridine reductase.
  - Dihydrobiopterin synthetase.
  - Carbinolamine dehydratase.

    "No need to memorise this one"

  } These enzymes maintain (BH4)

- Classical PKU is caused by PAH deficiency.
- Atypical PKU is caused by BH4 deficiency or the enzymes maintaining it.

Amino Acids and Tetrahydrobiopterin



BH4 is also required for :

- Tyrosine synthesis
- Conversion of tyrosine to dopa and catecholamines
- Conversion of tryptophan to serotonin

(Synthesis of catecholamines and serotonin which are neurotransmitters)

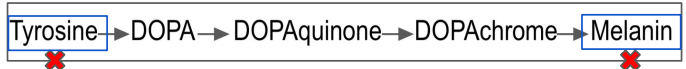
So, If there was a deficiency in BH4 or its enzymes, it will cause :

- Atypical PKU
- Serotonin deficiency
- Catecholamine deficiency

Characteristics of PKU

- In the absence of BH4 , Phe will not be converted to tyrosine.
- Melanin will become deficient because Tyrosine is required for synthesis of melanin.
- Deficiency of tyrosinase will lead to albinism.
- Causes light skin and photosensitivity in PKU patients.

Melanin Biosynthesis from Tyrosine



No or less tyrosine/ also inhibited by excess Phe

No or less melanin
Light skin in PKU patients

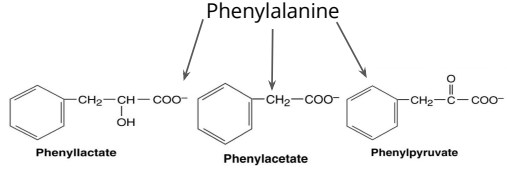
tip

You don't need to memorize the pathway

- Tyrosine will not be converted to catecholamines.
- Tryptophan will not be converted to serotonin as they both require BH4.
- Catecholamines and serotonin are neurotransmitters.

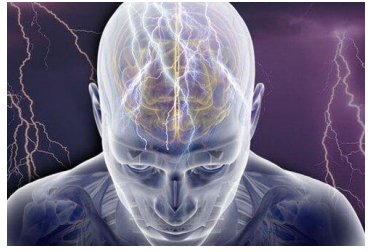
Look at the previous slide for more detail

- Elevated phenylalanine in tissues, plasma, urine.
- Phe is degraded to:
  - phenyllactate, phenylacetate, phenylpyruvate
- Gives urine a mousy odor.



Characteristics of PKU

CNS symptoms	Mental retardation, failure to walk or talk, seizures, microcephaly etc.
Hypopigmentation	Fair hair, light skin colour and blue eyes Melanin is not synthesized
Urine	Urine has a musty (mousy) odor



Diagnosis and Treatment of PKU

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Diagnosis:

- Prenatal "before birth" diagnosis is done by detecting gene mutation in fetus
- Neonatal diagnosis in infants is done by measuring levels of blood Phenylalanine
  We measure it after birth after 24-48 hours NOT immediately

Treatment:

- Lifelong phe-restricted diet
- Tyrosine supplementation

If the treatment is started before 7 days of birth, they might have a near normal life ,The problem is that phenylalanine is very abundant in most foods, so it is difficult to control.

Maple Syrup Urine Disease

- **Due to deficiency of branched chain α-ketoacid dehydrogenase**
- The enzyme decarboxylates:
  - Leucine
  - Valine
  - isoleucine

  } **(branched chain amino acids)**

Check out the next slide to understand the role of substrates and enzymes.

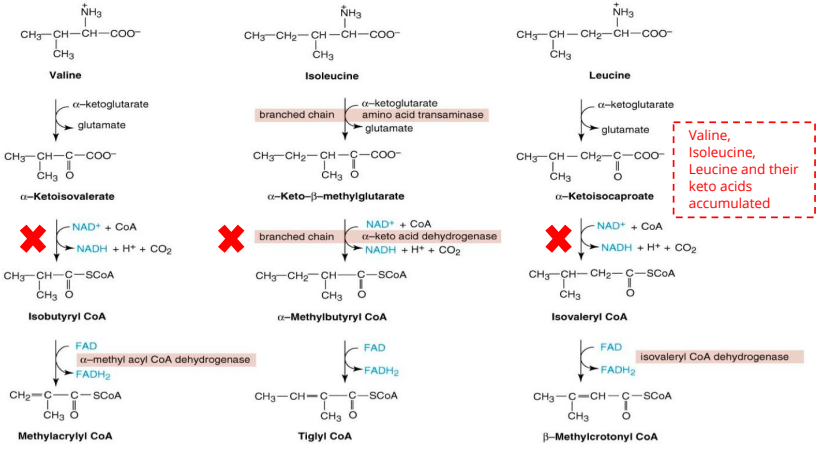
- These amino acids accumulate in blood
- Symptoms: mental retardation, physical disability, metabolic acidosis, etc.
- **Maple syrup odor of urine**

Deficiency of branched chain α-ketoacid dehydrogenase → accumulation of amino acids and their α-ketoacid (leading to metabolic acidosis).

Maple Syrup Urine Disease

No need to memorize structures or pathways.

You can read the notes to understand the role of the substrates and enzymes



Degradation of branched-chain amino acids: valine, isoleucine and leucine.
Deficiency of branched chain a-keto acid dehydrogenase leads to MSUD.

- In our body we have certain branched chain amino acids.
- **These amino acids are leucine, isoleucine and valine.**
- The first step in their degradation is deamination “we remove an amino group and introduce a ketone group at the alpha carbon”.
- By the end of this step, each amino acid is converted to its [α- keto acid].
- **The α- keto acids are acted on by their α- keto acid dehydrogenases.**
- If the α- keto acid dehydrogenase is deficient, it will lead to accumulation of the amino acids and their α- keto acid, leading to maple syrup urine disease (MSUD).

Maple Syrup Urine Disease

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Types:

Classic type:

- Most common (most severe)
- Due to little or no activity of branched chain α-ketoacid dehydrogenase

Intermediate and intermittent forms:

- Higher enzyme activity
- Symptoms are milder

Thiamine-responsive form:

- High doses of thiamine increases α-ketoacid dehydrogenase activity

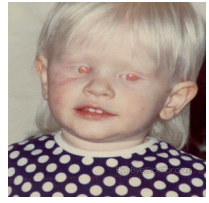
Thiamine-responsive form:
Activity of **α-ketoacid dehydrogenase** requires thiamine (COFACTOR).
Patient comes in with deficiency of the enzyme → by default you prescribe thiamine if the patient responds and his symptoms become milder, you put the patient in the 3rd category.

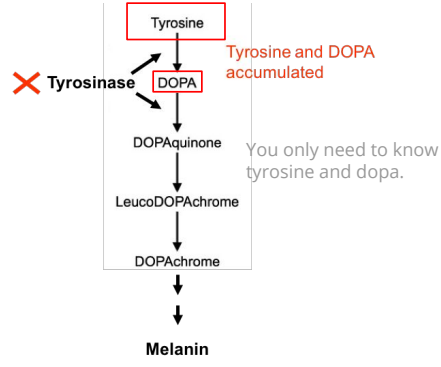
Treatment:

Limited intake of leucine, isoleucine and valine causes no toxic effects.
(We cannot restrict the intake entirely because these amino acids are essential for normal development.)

Albinism

- A disease of tyrosine metabolism
- Tyrosine is involved in melanin production
- Melanin is a pigment of hair, skin, eyes
- Due to tyrosinase deficiency
  (will lead to accumulation of tyrosine and dopa)
- Melanin is absent in albino patients
- Hair, skin, eyes appear white "eyes might appear red also"
- Vision defects, photophobia





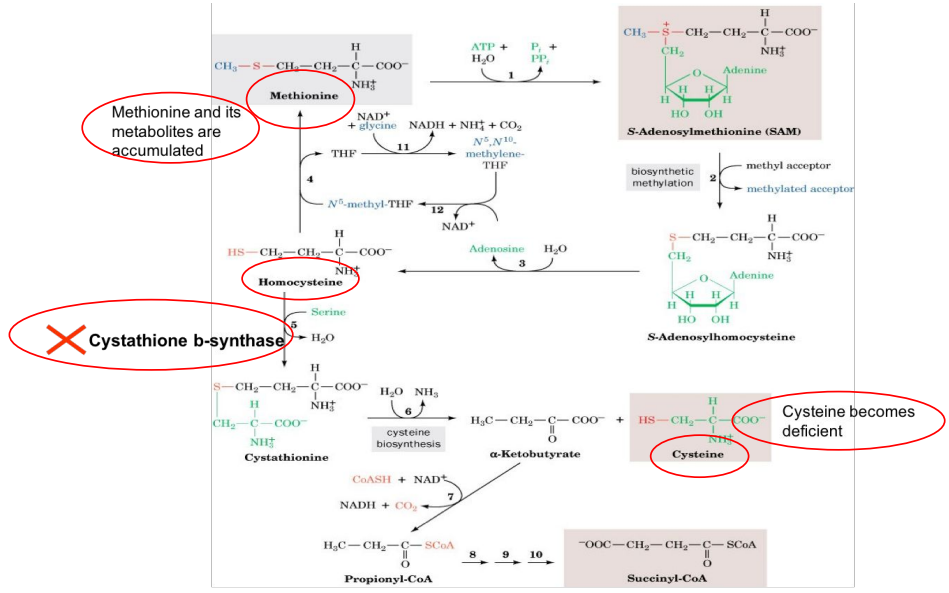
Melanin biosynthesis from tyrosine: Deficiency of tyrosinase leads to albinisim

Hypopigmentation in albinism is more severe than in phenylketonuria.
And the hypopigmentation in phenylketonuria is associated with CNS symptoms which are not found in albinism because tyrosine can be acquired by other sources.

Homocystinuria

- Due to defects in homocysteine (a non-standard amino acid) metabolism
- Deficiency of cystathionine β-synthase
  - Converts homocysteine to cystathionine
- High plasma and urine levels of homocysteine and methionine and low levels of cysteine.
  (High in blood and in urine)
- Homocysteine is a risk factor for atherosclerosis and heart disease.
  (If homocysteine is accumulated in blood it causes oxidative stress and is associated with inflammation and endothelial injury)
- Skeletal abnormalities, osteoporosis, mental retardation, displacement of eye lens.

If homocysteine is elevated in blood it is associated with low level of vitamin B12, B6 and folate [an active form of folic acid] . Studies have proved these vitamins causes homocysteine levels to go down.



Methionine degradation pathway: Deficiency of cystathione b-synthase leads to homocystinuria / homocysteinemia

What Dr.Sumbul said : **Don't skip this note**

Normally homocysteine is usually converted to

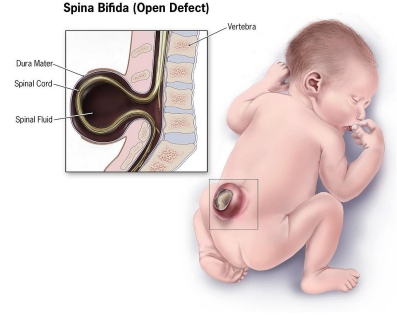
1. Methionine
2. Cysteine (a non-essential amino acid but when there is defect in enzyme it becomes essential) by the enzyme Cystathione β (beta)-synthase.

When cystathione β-synthase is deficient there will be an accumulation of methionine and homocysteine and cysteine is deficient.

cont.Homocystinuria

Hyperhomocysteinemia is also associated with:

- Neural tube defect (spina bifida incomplete closure of backbone)
- Vascular disease (atherosclerosis)
- A risk factor of heart disease



Treatment of Homocystinuria

- Oral administration of vitamins B_6,$B_{12}$and folate
  because homocysteine metabolism requires these vitamins
- Vitamin B_6 is a cofactor of cystathionineβ-synthase
- Methionine-restricted diet

Alkaptonuria

- A rare disease of tyrosine degradation
- Due to deficiency of homogentisic acid oxidase.*

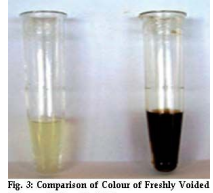
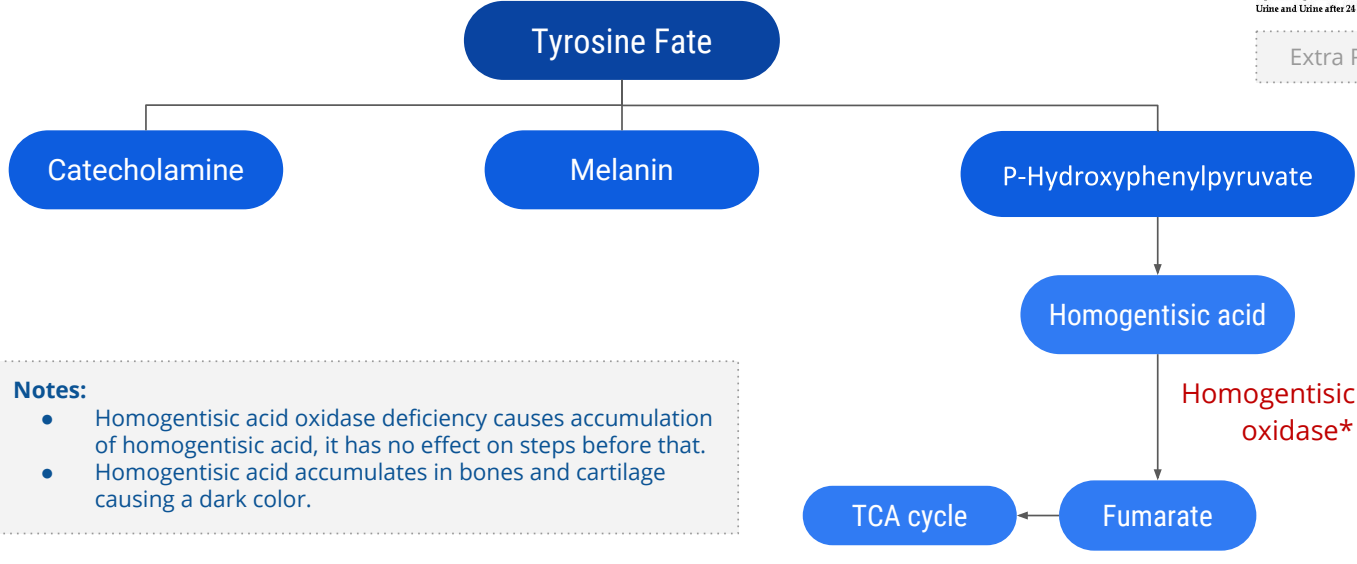


Fig. 3: Comparison of Colour of Freshly Voided Urine and Urine after 24 Hours

Extra Picture



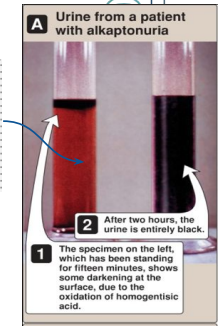
Notes:

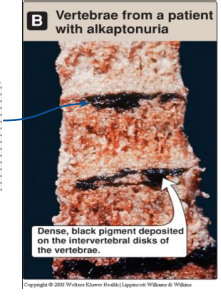
- Homogentisic acid oxidase deficiency causes accumulation of homogentisic acid, it has no effect on steps before that.
- Homogentisic acid accumulates in bones and cartilage causing a dark color.

Characteristics of Alkaptonuria

- Homogentisic aciduria: elevated homogentisic acid in urine which is oxidized to dark pigment over time.
- Arthritis.
- Black pigmentation of cartilage, tissue.
- Usually asymptomatic until adulthood.
  Up to the age of 40 the patient doesn't know that he/she has alkaptonuria, after that in late stages it shows as arthritis like symptoms and pain.
  In babies, the mother might notice change in the urine color in the diaper.

After 15 min the homogentisic acid reacts with the air causing a dark color





Dark because of accumulation of homogentisic acid

Treatment of Alkaptonuria

Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation.

Summary

IMPORTANT!

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Disease	Enzyme	Amino acid accumulated	Deficiency of	Symptoms	Treatment
Classical Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine	Tyrosine	• CNS symptoms • Hypopigmentation • Musty (mousy) odor of urine	Life long phenylalanine restricted diet and tyrosine supplementation.
Atypical Phenylketonuria	Dihydropteridine reductase Dihydrobiopterin synthetase		Tetrahydrobiopterin leading to non functioning phenylalanine hydroxylase		
Maple Syrup disease	Branched chain α-ketoacid dehydrogenase	Leucine, Isoleucine, Valine And their α-ketoacids	Products of Leucine, Isoleucine, Valine degradation pathways.	Mental retardation, physical disability, metabolic acidosis, maple syrup odor of urine.	Limited intake of leucine, Isoleucine, Valine.
Albinism	Tyrosinase	Tyrosine	Melanin	White hair, skin, and eyes. Vision defects, photophobia.	
Homocystinuria	Cystathionine β-synthase	Homocysteine and Methionine	Cysteine	Atherosclerosis, heart diseases, skeletal abnormalities, mental retardation.	Vitamins B6 & B12 and folic acid. Methionine-restricted diet.
Alkaptonuria	Homogentisic acid oxidase	Homogentisic acid	Fumarate	Dark urine pigment. Later stages: arthritis.	Restricted tyrosine & phenylalanine intake.

MCQs:

1-Which one of the following is symptome of Maple Syrup disease?

A) Atherosclerosis.
B) heart diseases.
C) all of them.
D) none of them.

2-Classic PKU is caused due to deficiency of:

A) phenylalanine hydroxylase.
B) Dihydrobiopterine synthetase.
C) Carbinolamine dehydratase.
D) Dihydropteridine reductase

3-Child diagnosed with alkaptonuria what is the only symptom you could find:

A) Homogentisic aciduria.
B) Arthritis.
C) black pigmentation in cartilage and tissue
D) both B and C.

4-Melanin is synthesized from:

A) Tyrosine.
B) Tryptophan.
C) cystathionine.
D) Methionine.

5-Albinism is disease of:

A) Tyrosine synthesis.
B) Tyrosine metabolism.
C) Tyrosine degradation.
D) none of them

6-Which on of the following is caused by deficiency of homogentisic acid oxidase?

A) Albinism.
B) Maple syrup Urine disease.
C) Alkaptonuria.
D) Phenylketonuria.

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

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Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- فيصل الطحان
- محمد الصويغ
- أنس القحطاني
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- محمد الاصقه
- نواف اللويمي
- معن شكر
- عبدالرحمن التركي

Girls team

- رهف الشنيبر
- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
- ريناد الغريبي
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