***Slide #2:***

Most important 3 coenzymes in amino acid metabolism are:

1-Pyridoxal phosphate (PLP, B6),

2-Tetrahydrofolate (FH4), folic acid, important for one-carbon transfer (if we want to transfer a methyl group)

3-Tetrahydrobiopterin (BH4) required for ring hydroxylation reactions (e.g., phenylalanine to tyrosine).

***Slide #3: synthesis of amino acids:***

We talked about essential & non essential amino acids.

***Slide #4***: degradation of amino acids:

\* Almost every amino acid will have a degradative pathway that can generate NADH.

\*Degradation classifies amino acids to:

A- Glucogenic

B- Ketogenic: amino acids that starts with the letter (L), Leucine&Lysine.

C- Both (glucogenic ketogenic):

\*Three of them have cycle form (have ring in their structures): Tyrosine, Tryptophan, and phenyl-alanine.

\*add isoleucine that is classified as both (glucogenic ketogenic).

***Slide #5***: ***degradation of amino acids:***

\*Breakdown of the carbon skeletons converge to form seven intermediate products, two of them are ketogenic (Acetyl CoA &Acetoacetate).

\*other intermediates are glucogenic.

\*these products are used in Synthesis of glucose, lipids&in production of energy.

***Slide#6: Amino acids that form oxaloacetate:***

1-aspartate 2-Asparagine

***Slide#7+8+9: α-Ketoglutarate related amino acids:***

1-glutamate

2-glutamine (which is related to glutamate)

3-proline: Glutamate converted to an aldehyde, spontaneously cyclizes followed by reduction to produce proline.

4-arginine forms urea & ornithine, if ornithine is in excess, transaminated to α-Ketoglutarate followed by another transamination to glutamate

Glutamate also go back to produce ornithine.

5-histidine: please refer to slide #9 to see the reactions.

\* Carbons of histidine come from glutmate, except one carbon that have nitrogen (formyl group).

\*One carbon that has nitrogen is called: Formimino.

\*the enzyme histidase will convert histidine to urocanate (urocanic acid).

\* In a series of steps, histidine is converted to N-Formiminoglutamate (FIGLU).

\* The subsequent reactions transfer one carbon of FIGLU to the FH4 pool and release NH4+ and glutamate.

\*remember that: Tetrahydrofolate (FH4): important for one-carbon transfer.

\* The FIGlu excretion test has been used in diagnosing a deficiency of folic acid.

\*histidine by a decarboxylation reaction gives histamine (enzyme used in this reaction: histidine decarboxylase).

***Slide#10***: ***pyruvate related amino acids:***

1-alanine:

\*corresponding ketoacid to alanine is pyruvate/transamination reaction/requires PLP, B6.

2-serine:

\*can be converted to pyruvate by serine dehydratase giving out ammonia group &water.

\*serine &pyruvate have three carbons in their structure.

3-glycine:

\*serine&glycines are converted to each other using the enzyme

(Serine hydroxymethyl-transferase).

\*the enzyme transfers a methyl group (on it a hydroxyl group).

\*the difference between **glycine & serine** is that:

- **Glycine:** the smallest amino acid, which contains only one carbon (α-carbon), hydrogen& R- group (which is hydrogen in glycine).

-**Serine**: have more one carbon (on it a hydroxyl group)

\*that’s why serine is a polar amino acid (hydroxyl group).

\*so this rxn we need Tetrahydrofolate (FH4) for the transfer of one carbon atom, as the carbon atom is transferred, is converted to.

***Slide#11: pyruvate related amino acids:***

4- Cystine & Cysteine:

\* **Cystine**: two Cysteines /disulfide bonds.

**\* Cystine reductase**: It gives electrons so that it will break down the disulfide bond that’s between the Cysteines.

\*every Cysteine takes hydrogen because it’s a reduction reaction.

\* Methionine will give homocysteine the sulfur group

.

\*serine will give homocysteine the carbons

.

\*now cystathionine is produced. (Reaction in slide #11)

\* **Cystathionine** will be converted to **Cysteine**.

\*Carbons of Cysteine from: **serine**.

\*sulfur group of Cysteine from: **methionine**.

\* Cysteine is **Not** an essential amino acid.

\* Cysteine essentiality is governed by methionine.

\*if you are taking in diet more Cysteine, so you **do Not**  need to break down Methionine to give Cysteine.

\*then you are **sparing Methionine**, so excess diet have **a sparing effect** on methionine.

\*how Cysteine is degraded? By the liver enzymes , desulfurase which produces hydrogen sulfide (H2S) & pyruvate.

***Slide#12:*** ***pyruvate related amino acids:***

**5-threonine:**

\*in its degradation pathway it gives **α-ketobutyrate.**

**\* α-ketobutyrate always gives you propionyl CoA &at the end it give us succinyl CoA.**

\*SO α-ketobutyrate is **glycogenic**.

\*so threonine is degraded by **threonine dehydratase** to give **ammonia** which convertes to **α-ketobutyrate.**

\* α-ketobutyrate undergoes **decarboxylation** &give propionyl CoA
.

\*by the addition of carboxylic group we have to use **biotin (vitamin B7))** & we have now .

\*  is converted to **succinyl** **CoA**(using vitamin B12 in this reaction).



***Slide #13*** ***:( amino acids that form fumarate):***

1-**aspartate**:

\*it gives fumarate in the urea cycle the rxn is:

Arginosuccinate L-Arginine

Fumarate

**\*carbons of fumarate are from aspartate.**

2- phenylalanine & tyrosine :

**\* phenylalanine & tyrosine differs that tyrosine has a hydroxyl group.**

**\*pathway of phenylalanine is the same as tyrosine.**

\* Phenylalanine is converted to tyrosine (enzyme that is used is: phenylalanine hydroxylase/coenzyme used **Tetrahydrobiopterin (BH4)** which is important for **ring hydroxylation.**

\* Phenylalanine &tyrosine pathway (you should now the intermediates because they are related to diseases to be discussed later in the sheet.

\* refer to the pathway in slide #13

\***homogentisate** after a series of reactions give you **fumarate** (glucogenic)& **Acetoacetate** (ketogenic).

\*defect in phenylalanine hydroxylase (this enzyme which convert phenylalanine to tyrosine) so as a result we will **not** have tyrosine, but we will have accumulation of phenylalanine. This disease is called **PKU**.

\*Tyrosine p-hydroxyphenylpyruvate (the enzyme used in this reaction is tyrosine aminotransferase, when there is a defect in this enzyme the disease called **tyrosinemia II.**

\*there is another disease called tyrosinemia I.

\* Homogentisate: we will talk about it in disease called **alcaptonurea**.

\*the material that oxidizes homogentisic acid(homogentisate) is called homogentisate oxidase.

***Slide#14(amino acid that form succinyl CoA )***

1-Methionine is degraded to form α-Ketoglutarate by the enzyme **methionine dehydratase** and it will give the amino group out.

\* α-Ketoglutarate will give propionyl CoA.

\* **Four** amino acids will give ***propionyl CoA***:

1- Methionine

2-Threonine

3-Valine

4-Isoleucine

\*as there is propionyl COA there will be at the end succinyl CoA .(so these four amino acids are **glucogenic** .

\* Propionyl CoA is carboxylated (requires biotin) to form methylmalonyl CoA

\* Methylmalonyl CoA then converted to succinyl CoA (requires vitamin B12).

***Slide#15(amino*** ***acid that form succinyl CoA )***

\* ***Methionine*** is converted to SAM(S-adenosylmethionine) .

\*SAM **differs** from methionine that SAM has **Adenosine** (this adenosine is from ATP).

\*ATP has 3 phosphate groups, but SAM dose Not have any phosphate group so the reaction needs hydrolysis of the 3 phosphate bonds that are in the ATP.

\* If I break one phosphate it will give 2 phosphates, and those will break to pyrophosphate for more energy (reaction need high energy).

\*When 3 phosphates are removed we will have adenosine alone, this adenosine will attach to sulfur that is in methionine.

\*Methionine is not reactive, because the sulfur is between 2 carbon atoms.

\* Adenosine from ATP that will attach to sulfur, so that it is called (S-adenosylmethionine) so the attachment of adenosine will weaken the bond between sulfur &carbon.

\* the terminal CH3 that is in the methionine will become reactive, it can go and attack other structures.

\* SAM → S-adenosylhomocysteine (SAH)…as the carbon in SAM will be reactive it will go and attack another structures it will be converted to SAH.

\*SAH as adenosine is removed its converted to homocysteine .

\* **Homocysteine** as a common intermediate it can continue in the pathway to give succinyl CoA **or** homocysteine can give methionine.

\* What is the difference between homocysteine and methionine?

Methionine has a CH3 group.

\*How can I add a methyl group on homocysteine so that it will be converted to methionine?

By using (FH4 & vitamin B12) because there will be transfer of one methyl group.

**\*Homocysteine has more one carbon atom than Cysteine.**

***Slide #17***:

\*Homocysteine as a material is related to cardiovascular disease (as total plasma of homocysteine increases, cardiovascular mortality increase).

\*homocysteine results in:
 1-Oxidative damage,,, 2-Inflammation ,,,,3-Endothelial dysfunction, at the end occlusion of arteries will occur.

\*Risk of homocysteine is **independent** more any other factors (if there is other factors risk will remain the same)……(risk in **not** linked to other factors).

\*There is a study: Mild elevations of homocysteine are seen in ≈ 7% of the population.

\*Plasma homocysteine levels are **inversely** related to (folate, B12, & B6), *because* these vitamins are required in the conversion of homocysteine to methionine or Cysteine.

\* If we give supplements by these vitamins (folate, B12, & B6), as there plasma concentrations increases, the homocysteine will be less, so as a result cardiovascular mortality will be less. But this case does not happen, as they give the supplement the cardiovascular mortality stays the same (it does not decrease).

\* So because homocysteine does **Not** decrease after the supplements this means that homocysteine is not a cause of cardiovascular diseases.

**\* Homocysteine is a marker for the disease (it's an outcome not a cause).**

***Slide#18((amino acid that form succinyl CoA)***

**2-valine &isoleucine:**

\*leucine is **ketogenic** so the pathway will give:-***Acetoacetate*** &***acetyl*** ***CoA***.

(((it will NOT give propionyl CoA or succinyl CoA or fumarate or other glucogenic intermediate) )).

\*leucine, valine &isoleucine are branched chain amino acids.

\*branched chain amino acids (R group is branched/they have common pathway in degradation).

\* Leucine, valine &isoleucine undergoes ***transamination*** (vitamin B6 is required) & that gives there corresponding ketoacid. (Enzyme used in this reaction: branched-chain α-amino acid aminotransferase.

\*after they are transaminated into ketoacids, **decarboxylation** will occur (enzyme used in this reaction:α-keto acid dehydrogenase)/(co2 is out)/electrons are transferred on NAD+ to give NADH)

\*those enzymes :

1- α-Ketoglutarate dehydrogenase complex

2-pyruvate dehydrogenase complex

3-branched chain α-keto acid dehydrogenase complex.

**\*Output of all these enzymes is CoA.**

\*Pyruvate will give acetyl CoA.

\* α-Ketoglutarate ( 5 carbon atoms) will give succinyl CoA(4 carbon atoms).

\* α-keto acid dehydrogenase complex (if there is a deficiency in this enzyme/or its efficiency isn’t normal),…accumulation of ketoacid and there corresponding amino acid because the reaction is reversible )

This will cause a disease which is **maple syrup urine disease.**

\***maple disease:** increase in the concentration of ketoacid and there corresponding amino acid as there is deficiency in α-keto acid dehydrogenase complex. so the urine in this disease smell sweet.

\*Decarboxylation Reaction will give NADH & FADH2 are generated (energy).

\*after decarboxylation reaction products will be:

1-**leucine**(ketogenic amino acid) will give acetyl CoA /Acetoacetate (ketogenic).

2-**isoleucine**(mixed) will give acetyl CoA (ketogenic)&propionyl CoA(glucogenic)

3-**valine**:(glucogenic):it will give propionyl CoA.

***SLIDE #19(amino acids that form acetyl CoA & Acetoacetate (ketogenic):***

**1-Tryptophan (MIXED):**

\*its structure has two rings & a carbon skeleton which is the backbone of the amino acid.

\*carbons that are **not** in ring is like the structure of **alanine** but alanine has a methyl group as an R group.

\*alanine will get out from the carbons that are not in the structure of a ring.

\*carbons in the ring of tryptophan will give acetyl CoA (ketogenic) ,

\* Tryptophan will give Alanine which is (glucogenic) because it will give pyruvate.

\*tryptophan is mixed☺

\*structure of tryptophan is **close** to the structure of **niacin** (**vitamin B3).**

\* NAD+ & NADP+ can be produced from the ring structure of tryptophan (niacin requirements)

\*niacin requirements differs as the ingestion (intake of tryptophan) differs.

\*you can use the ring of tryptophan (tryptophan is an essential amino acid) to produce niacin.

***Slide#20((amino acids that form acetyl CoA & Acetoacetate (ketogenic):***

2-Phenylalanine and Tyrosine:

\*As phenylalanine is converted to tyrosine (Phenylalanine hydroxylase (PAH) is used. Requires molecular O2(added to the ring) and BH4(ring hydroxylation)

\*please look to the steps of the pathway in slide#20.

***Slide#21((amino acids that form acetyl CoA & Acetoacetate (ketogenic):***

3- Leucine, isoleucine, lysine

\* leucine (ketogenic amino acid) will give acetyl CoA /Acetoacetate

\* isoleucine (mixed) will give acetyl CoA (ketogenic)&propionyl CoA(glucogenic)

\*lysine (ketogenic) will give acetyl CoA.

\* Leucine during its degradation produces hydroxymethylglutaryl CoA (HMGCoA), which is cleaved to form **acetyl CoA** and **Acetoacetate**.

***Slide#22(synthesis of non essential amino acids):***

A-Synthesized from intermediates of metabolism or, as in the case of tyrosine(from phenylalanine) & Cysteine(from methionine).

B- Synthesis from α-keto acids:

1. Alanine from pyruvate,
2. Aspartate from oxaloacetate
3. glutamate from α-Ketoglutarate

C-Synthesis by amidation (addition of (C-N)

Which is an amide bond) as in: Glutamine & Asparagine.

D-Proline: Glutamate converted to proline by cyclization & reduction reactions (reduction of glutamate then spontaneous ring formation then another reduction)

E- Serine, glycine, & Cysteine:

\*Serine: from glycine (serine hydroxymethyl transferase)

\*Glycine: from serine (serine hydroxymethyl transferase)

\* Cysteine: from homocysteine & serine.

F- Tyrosine: from phenylalanine.

***slide#23: metabolic defects in amino acid metabolism:***

\*as there are enzymes, deficiency is possible/mutation in the gene is possible/enzyme is **not** completely affected **or** enzyme is **not** presented is also possible.

***SLIDE#24: PHENYLKETONURIA (PKU):***

\*Deficiency of phenylalanine hydroxylase:
 this enzyme that adds *hydroxyl group* to **phenylalanine** so that it will be converted to **tyrosine**.

\* if this enzyme is deficient or its efficiency not 100 %( phenylalanine will increases /tyrosine is very low or not presented)

\*if phenylalanine is accumulated &can't be converted to tyrosine, it will be converted to other intermediates that have effects on the **CNS** (mental retardation by year one after birth).

\* phenylalanine it will be converted to tyrosine by the use of BH4(Tetrahydrobiopterin) that is after oxidation reaction converted to BH2(dihydrobiopterin).

\***Reformation** of BH4 will happen as a **cycle** because coenzyme must be returned to normal) and the reformation will happen by the enzyme:

(Dihydropteridine reductase) that adds two hydrogen atoms to BH2 to be converted to BH4.

\*deficiency can occur in:

1- Phenylalanine hydroxylase

2- Dihydropteridine reductase (the enzyme that regenerate coenzyme BH4, without coenzyme, the enzyme phenylalanine hydroxylase will not work).

\*route of phenylalanine is to give you tyrosine but sometimes it can give other routes.

***\*the routes are:***

1-tyrosine that is converted to phenylalanine

2- Tyrosine that is converted to dopamine or epinephrine.

3-tryptophan that is converted to serotonin

\*so if there is a problem to regenerate the coenzyme BH4 …**all** neurotransmissions will be affected because neurotransmitters (dopamine, epinephrine serotonin are affected.

***SLIDE#25(PHENYLKETONURIA (PKU)***

\* Phenylalanine can be converted to tyrosine.

\* Phenylalanine can **Not** be converted or can be converted but in very low amount to phenylpyruvate or to phenyl lactate or to phenyl acetate.

\*when the enzyme Phenylalanine hydroxylase is deficient ,so phenylpyruvate / phenyl lactate / phenyl acetate are produced in high amounts (glucogenic),they will accumulate in brain and cause mental retardation ,failure to walk or talk.

\*in PKU we have to do screening (24-48 hours) after birth so the mother will let him get rid of the defective enzymes through the placenta .

\* Untreated PKU typically shows symptoms of mental retardation by year 1 (neonatal screening, 24 to 48 hours of protein feeding because the baby starts doing metabolism.

\*hydroxylation of tyrosine by tyrosinase is the *first* step in the formation of pigments.

\*if tyrosinase is deficient or any other enzyme in the pathway of conversion from tyrosine to melanin, **hypopigmentation** will occur (**albinism**)

\*for any amino acid deficiency, we should decrease the amino acid or protein contents.

\* Treatment is easy as know the deficiency in childhood.

\*PKU treatment: don’t give phenylalanine that’s in aspartame (which is used to sweet cokes, gums)

\*aspartame contains two amino acids (phenylalanine and aspartic acid)

***Slide#26(MAPLE SYRUP URINE DISEASE)***

\* Partial/complete deficiency (branched-chain α-keto acid dehydrogenase

\* These amino acids and their corresponding α-keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions.

\*urine smells sweet.

\* If untreated, leads to mental retardation, physical disabilities, & even death.

\*treatment: synthetic formula - limited amounts of leucine, isoleucine, and valine should be sufficient.

***Slide#27(HOMOCYSTINURIA***)

\* The **most common cause of** **homocystinuria** is a defect in the enzyme **cystathionine β-synthase**, which converts homocysteine to cystathionine.

(Reaction requires B6)

\* Patients can be responsive or nonresponsive to oral pyridoxine (B6)—a coenzyme of cystathionine β-synthase

\* Responsive patients usually have a milder and later onset of clinical symptoms.

***SLIDE#28(ALBINISM***)

\*albinos differ in the degree of the disease:

1- Complete albinism: deficiency in any enzyme that gives melanin

2-partial deficiency: melanin is less.

\* Complete albinism - rare (the most severe form of the condition) results from a complete deficiency of tyrosinase activity, causing a total absence of pigment from the hair, eyes, and skin.

\* In addition: vision defects and photophobia and high risk for skin cancer because nothing prevents UV light from entering.

***Slide#29(ALKAPTONURIA):***

\* Deficiency in homogentisic acid oxidase → accumulation of homogentisic acid (degradative pathway of tyrosine).

\*symptoms:

1- Homogentisic aciduria (elevated levels of homogentisic acid, which is oxidized to a dark pigment)

2- Large joint arthritis

3- Black ochronotic pigmentation of cartilage & collagenous tissue

\* Although alkaptonuria is **not** life-threatening, the associated arthritis may be severely crippling (patient can't walk).

\*treatment: Diets with **low (sufficient but not excess)**  in protein— especially **Phe** & **Tyr**.

\*test tube for alkaptonuria patient with time its oxidized &turned black.

1-after 15 minutes urine is dark.

2-after 2 hours urine is entirely black.

\*in babies you can know that they are alkaptonuria patients from there diapers (blackish material on them).

\*always when amino acid in excess, degradation starts, so we must take the amino acids in sufficient

\***maple syrup** disease is **NOT** related to tyrosine while other diseases are related to tyrosine.



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