Faculty of Science
Beni-Suef University
Egypt

Inborn Errors of Metabolism

Part 2 (Inborn Errors of Amino Acids and Fatty Acids Metabolism)

Prepared by

Prof. Dr. Osama Mohamed Ahmed

Professor of Physiology, Beni-Suef University

For
Biochemistry Diploma Students

2013-2014

ISBN: 978-977-90-1206-3 Legal Deposit Number: 2013/22719

[Inborn errors of metabolism are rare genetic disorders in which a single gene defect causes a clinically significant block in a metabolic pathway resulting either in accumulation of substrate behind the block or deficiency of the product.]

Contents

Amino acid metabolism disorders

These disorders include:

- Phenylketonuria
- Tyrosinemia
- Alkaptonuria
- Hyperhomocysteinemia
- Maple Syrup Urine Disease
- Glutaric acidemia (aciduria) type I
- Hyperammonemia (It is also a defect in ornithine cycle).

Phenylketonuria

It is caused by a mutation in phenyl hydroxylase gene. It is autosomal recessive with gene map locus: 12q24.1. The disorder is characterized by accumulation of phenylalanine and phenylketone due to deficiency of phenylalanine hydroxylase, the rate-limiting step in phenylalanine catabolism. The accumulation of phenylalanine activates alternate pathway to form phenylpyruvate as well as Phenylketone (Figure 1).

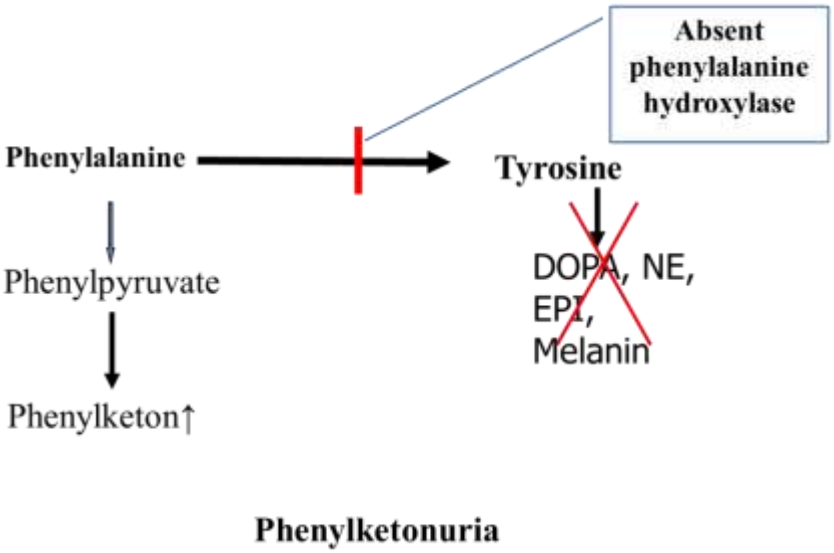

Figure 1: Phenyl alanine hydroxylase deficiency

Incidence

United States Caucasians are affected at a rate of 1 in 10,000. Turkey has the highest documented rate in the world, with 1 in 2,600 births, while countries such as Finland and Japan have extremely low rates with fewer than one case of PKU in 100,000 births.

Signs and symptoms

Signs and symptoms include:

1- Severe mental retardation.

2- Brain Damage

3- Seizure

Treatment and management

The strategy of Treatment and management include two lines which are:

- Low phenylalanine and rich tyrosine in diet (Figure 2).
- Aspatame must be avoided because aspatame is formed of phenylalanine and aspartate.

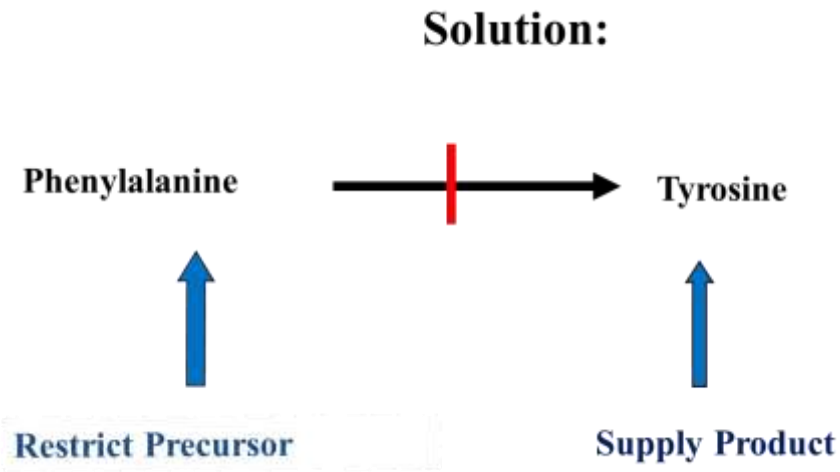

Figure 2: Low phenylalanine and rich tyrosine in diet to solve the problem of phenylketonuria

Tyrosinemia

Tyrosinemia is an inborn error of metabolism in which the body cannot effectively break down the amino acid tyrosine. Its inheritance is autosomal recessive. Most inborn forms of tyrosinemia produce hypertyrosinemia (high levels of tyrosine). Symptoms of this inborn error include liver and kidney disturbances and mental retardation. If untreated, tyrosinemia can be fatal.

There are three types which are:

1) Tyrosinemia type 1
2) Tyrosinemia type 2
3) Tyrosinemia type 3

Tyrosinemia type I

It is also known as hepatorenal tyrosinemia. It is an autosomal recessive disorder of gene map locus is 15q23-q25. It is caused by deficiency of fumarylacetoacetase (FAH; Fumaryl acetoacetate hydrolase), the last enzyme of tyrosine degradation.

Metabolic Defect

The metabolic defect results from a deficiency of fumarylacetoacetate hydrolase or fumarylacetoacetase (FAH) in liver and proximal convoluted tubules. Fumarylacetoacetate hydrolase catalyzes the final step in the degradation of tyrosine - fumarylacetoacetate to fumarate, acetoacetate and succinate. The FAH deficiency leads to accumulation of fumaryl acetoacetate and tyrosine in liver and proximal convoluted tubules (Figure 3).

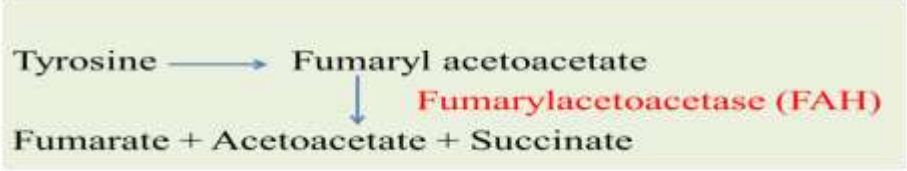

Figure 3: Reaction activated by fumaryl acetoacetate hydrolase (FAH)

Pathophysiology

Fumarylacetoacetate accumulates in hepatocytes and proximal renal tubal cells and causes oxidative damage and DNA damage leading to cell death and dysfunctional gene expression which alters metabolic processes like protein synthesis and gluconeogenesis. The increase in fumarylacetoacetate inhibits previous steps in tyrosine degradation leading to an accumulation of tyrosine in the body. Tyrosine is not directly toxic to the liver or kidneys but causes dermatologic and neurodevelopmental problems.

Incidence

Worldwide, type I tyrosinemia affects about 1 person in 100,000. This type of tyrosinemia is much more common in Quebec, Canada. The overall incidence in Quebec is about 1 in 16,000 individuals.

Diagnosis

Diagnosis and testing can be performed by

- Detection of fumarylacetoacetase (FAH) in blood or in biopsies of liver and kidney cortex.
- Detection of tyrosine and fumarylacetoacetate in these tissues.

Signs and Symptoms

They include:

- Progressive liver and kidney dysfunction
- Hepatomegaly
- Liver cirrhosis
- Conjugated hyperbilirubinemia
- Elevated AFP, hypoglycemia and coagulation abnormalities.
- An increased risk of hepatocellular carcinoma
- Renal tubular acidosis, hypophosphatemia and aminoaciduria.
- Cardiomyopathy, neurologic and dermatologic manifestations are also possible

Treatment

The primary treatment for type 1 tyrosinemia is nitisinone (Orfadin). Nitisinone inhibits the conversion of 4-OH phenylpyruvate to homogentisic acid by 4-OH phenylpyruvate dioxygenase, the second step in tyrosine degradation. By inhibiting this enzyme, the accumulation of the fumarylacetoacetate is prevented. Previously, liver transplantation was the primary treatment option and is still used in patients in whom nitisinone fails.

Tyrosinemia type II

It is also known as oculocutaneous tyrosinemia, Richner-Hanhart syndrome. It is an autosomal recessive disorder of gene map locus: 16q22.2. It is caused by deficiency of Tyrosine Aminotransferase (TAT; Tyrosine Transaminase). Tyrosine aminotransferase is the first in a series of five enzymes that converts tyrosine to smaller molecules, which are excreted by the kidneys or used in reactions that produce energy. It catalyzes the conversion of tyrosine to 4 hydroxyphenylpyruvate (Figure 4).

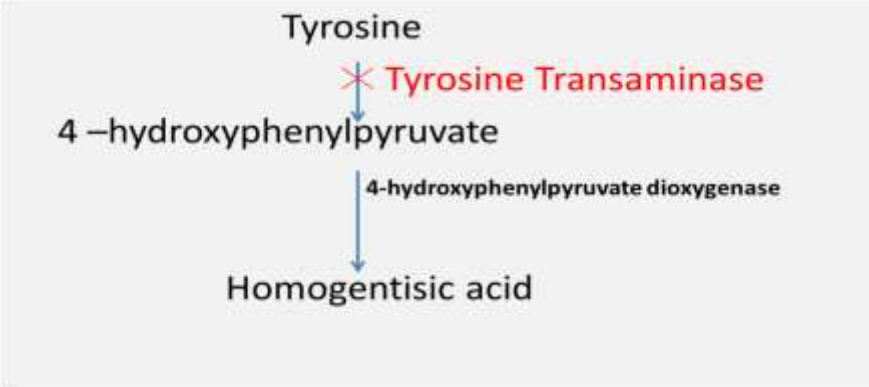

Figure 4: Deficiency of tyrosine transaminase (TAT)

Clinical Signs and Symptoms

This form of the disorder can affect the eyes, skin, and mental development.

Symptoms often begin in early childhood and include:

- excessive tearing,
- abnormal sensitivity to light (photophobia),

- eye pain and redness,
- painful skin lesions on the palms and soles, and
- about half of individuals with type II tyrosinemia are also mentally challenged.

Incidence

Type II tyrosinemia occurs in fewer than 1 in 250,000 individuals.

Tyrosinemia type III

Tyrosinemia type III is an autosomal recessive disorder characterized by elevated levels of blood tyrosine and massive excretion of its derivatives into urine. Its gene map locus is 12q24.31. It is caused by a deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase. This enzyme converts dioxygenase (HPD) converts a tyrosine byproduct called 4-hydroxyphenylpyruvate to homogentisic acid (Figure 5). The enzyme is abundant in the liver, and smaller amounts are found in the kidneys.

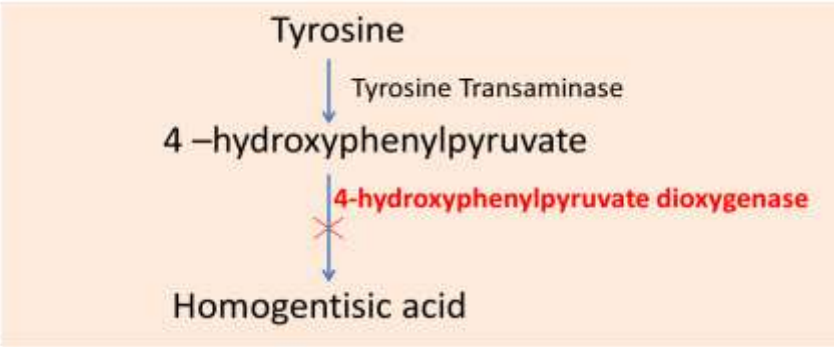

Figure 5: deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase

Clinical Signs and Symptoms

- mental retardation,
- convulsions, with the absence of liver damage,
- seizures, and
- periodic loss of balance and coordination (intermittent ataxia)

Incidence

Type III tyrosinemia is very rare; only a few cases have been reported. It is rarer than types I and II.

Alkaptonuria

Alkaptonuria is also called a black urine disease or an alcaptonuria. It is a rare autosomal recessive inherited genetic disorder of phenylalanine and tyrosine metabolism. It is due to a defect in the enzyme homogentisate 1,2-dioxygenase, which participates in the degradation of tyrosine. As a result, homogentisic acid and its oxide, called alkapton, accumulate in the blood and are excreted in urine in large amounts (hence -uria).

Metabolic defects

Tyrosine is converted by transaminase into 4- hydroxyphenyl pyruvic acid. The later is biotransformed to homogentisic acid by 4- hydroxyphenyl pyruvic acid dioxygenase. Deficiency of homogentisate 1,2-dioxygenase, the 1st enzyme that degrade homogentisic acid into its by-products leads to accumulation of homogentisic acid (Figures 6, 7 and 8).

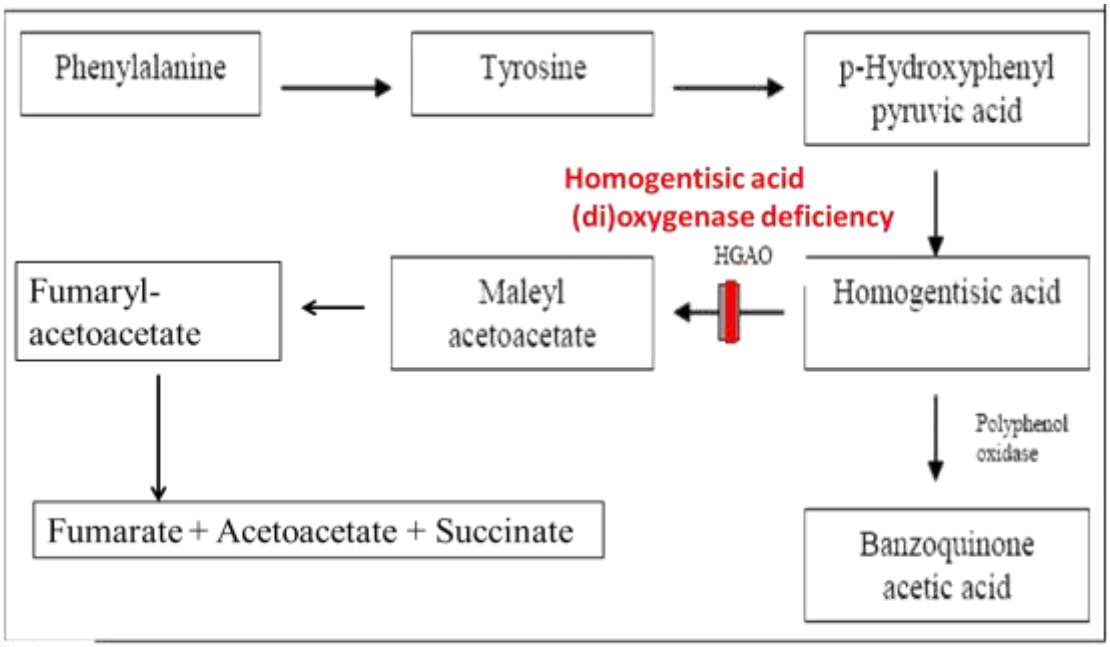

Figure 6 : Showing metabolic pathway of phenylalanine, tyrosine and HGA and the site of metabolic block responsible for AKU.

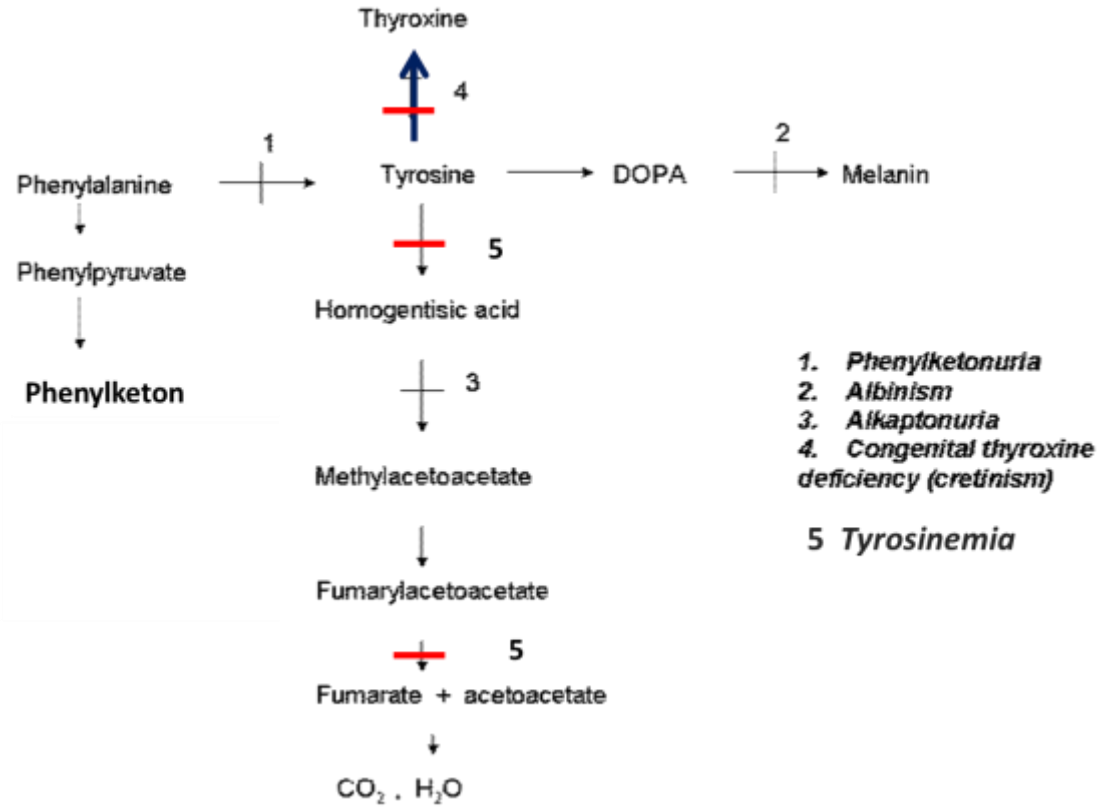

Figure 7: Deficiencies of different enzymes that activates various pathways phenylalanine and tyrosine metabolism

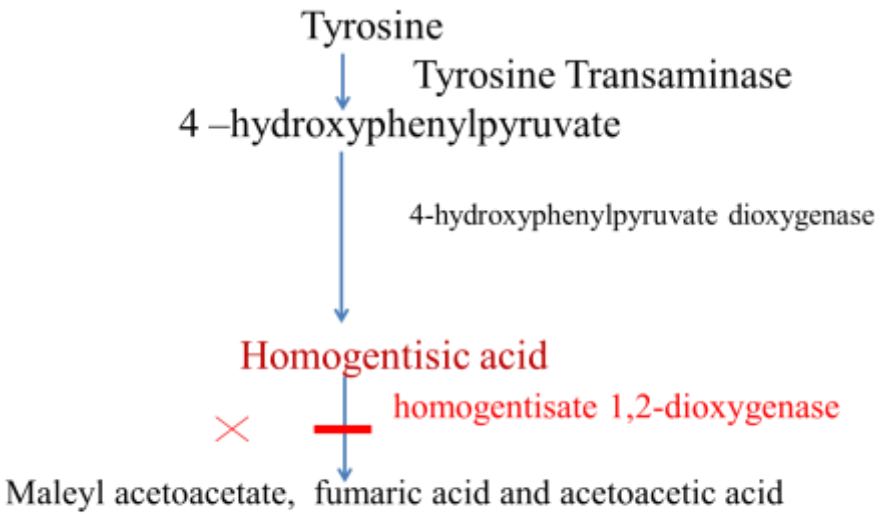

Figure 8: Deficiency of homogentisate 1, 2-dioxygenase leading to accumulation of homogentisic acid

Pathogenesis

Excessive homogentisic acid causes damage to cartilage (ochronosis, leading to osteoarthritis) and heart valves as well as precipitating as kidney stones.

Genetic defect

Alkaptonuria ia an autosomal recessive metabolic disorder and is is caused by mutation in the homogentisate 1,2-dioxygenase gene (HGD; 607474) at Gene map locus: 3q13.33

Clinical signs and symptoms

The main symptoms of alkaptonuria are due to the accumulation of homogentisic acid in tissues. Clinical signs and symptoms (Figure 9) include:

- Urine turns dark on standing and alkalinization.
- Ochronotic pigmentation of cartilage and collagenous tissues, and arthritis, especially characteristic in the spine.
- Damage to cartilage (ochronosis, leading to osteoarthritis) and heart valves as well as precipitating as kidney stones.
- The sclera of the eyes may be pigmented (often only at a later age)
- Ear wax exposed to air turns red or black (depending on diet) after several hours because of the accumulation of homogentisic acid
- More pronounced narrowing and calcification at all intervertebral spaces, demonstrating the progressive nature of alkaptonuria.
- Coronary artery disease may be accelerated in alkaptonuria
- Valvular heart disease, mainly calcification and regurgitation of the aortic and mitral valves, may occur, and in severe and progressive cases.

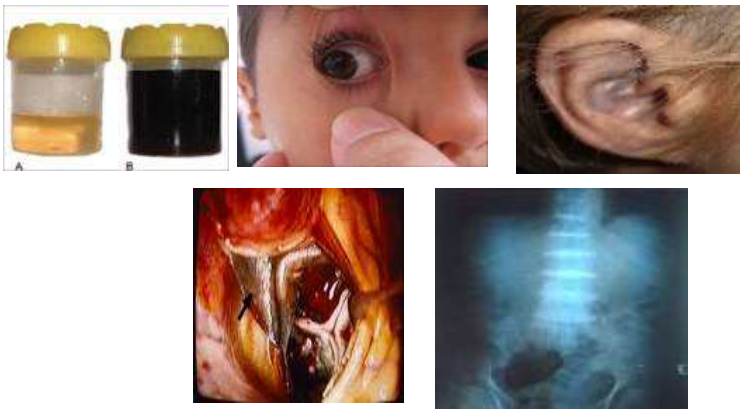

Figure 9: Clinical signs and symptoms. The main symptoms of alkaptonuria are due to the accumulation of homogentisic acid in tissues.

Epidemiology

In Slovakia the disease occurs in 1:19,000 people. In other ethnic groups, the normal prevalence is between 1:100,000 and 1:250,000. It is reported frequently in the Dominican Republic, but exact prevalence there is not known

Diagnosis

Alkaptonuria can be diagnosed by detection of homogentisic acid in blood plasma and urine and deficiency of homogentisate 1,2-dioxygenase.

Management and treatment

High doses of ascorbic acid may prevent deposition of the polymerized ochronotic pigment and may therefore prevent or delay subsequent symptoms. Low protein diet especially low in phenylalanine and tyrosine is advocated in combination with ascorbic acid. A new medicine - Nitisinone that inhibits 4-hydroxyphenylpyruvate dioxygenase, the enzyme that generates homogentisic acid from 4-hydroxyphenylpyruvic acid, is on trial for the evaluation of long-term therapy.

Hyperhomocysteinemia (Homocysteinemia) and Homocystinuria

Homocysteinemia refers to above-normal concentrations of plasma/serum homocysteine (Figure 10). Homocysteinemia is a feature of several inherited metabolic disorders, including:

1) Homocystinuria, due to mutation in the CBS gene (deficiency of cystathionine beta-synthase) (Figure 11 and 12).
2) Homocystinuria, due to N(5,10)-methylenetetrahydrofolate reductase deficiency, caused by mutation in the MTHFR gene (Figure 11 and 12).
3) Homocysteinemia/homocystinuria and megaloblastic anemia can result from defects in vitamin B12 (cobalamin; cbl) metabolism.

Deficiency of vitamin B12 (Cobalamin), Vitamin B9 (folic acid) and vitamin B6 (pyridoxin) in diet may result in homocysteinemia.

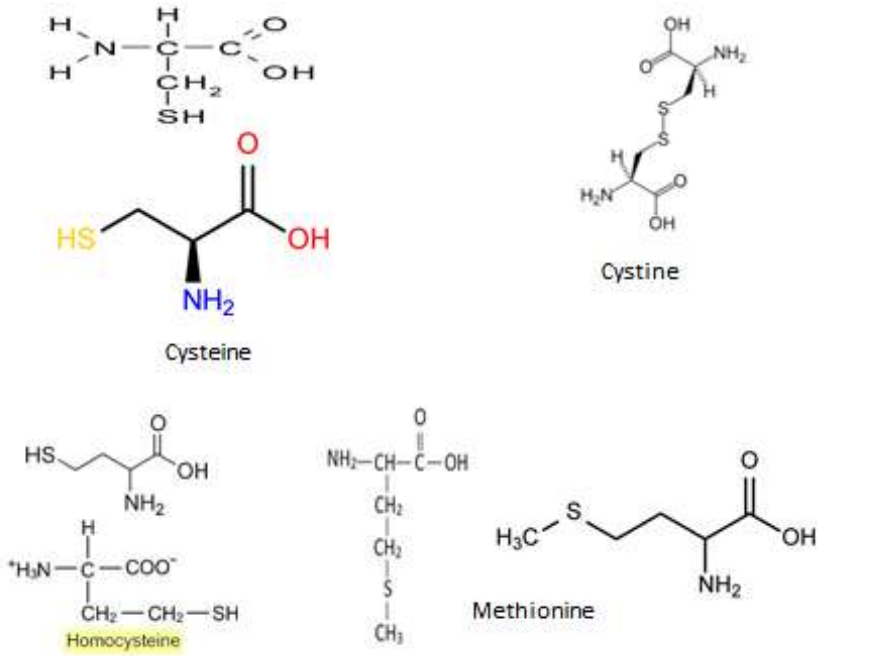

Figure 10: Sulphur containing amino acids

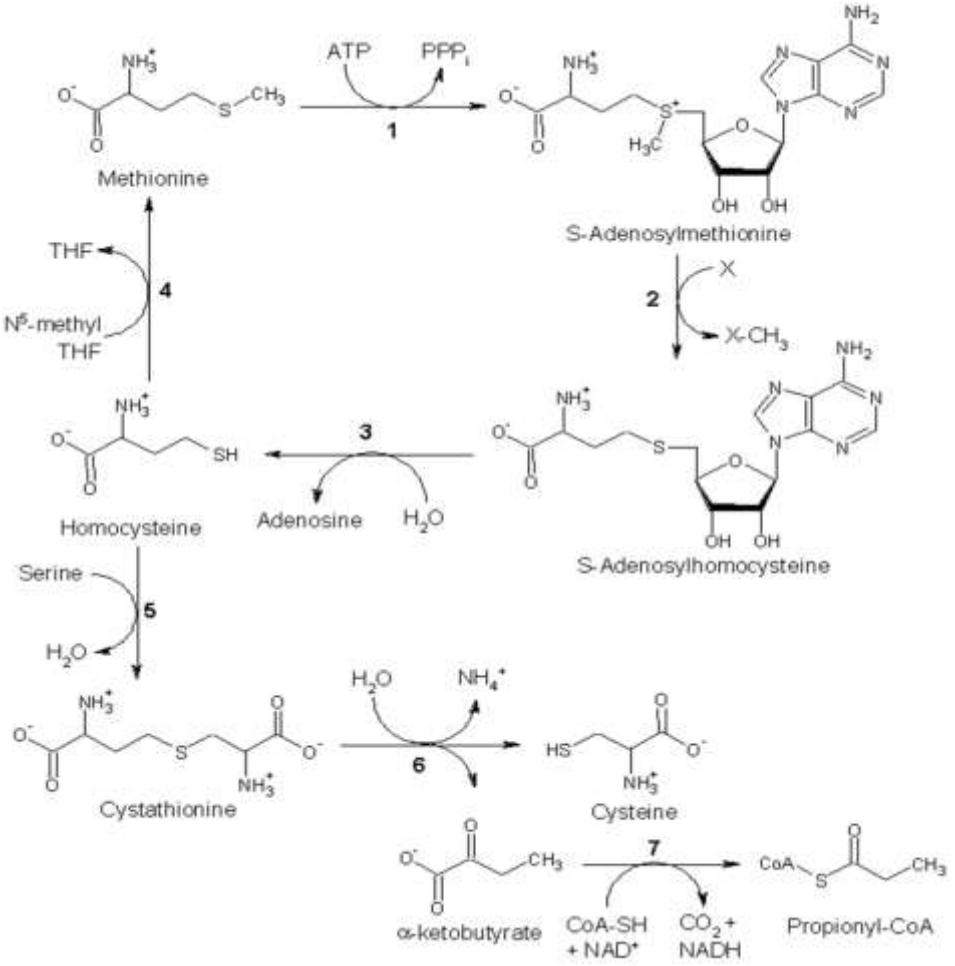

Figure 11: Metabolic pathways of homocysteine

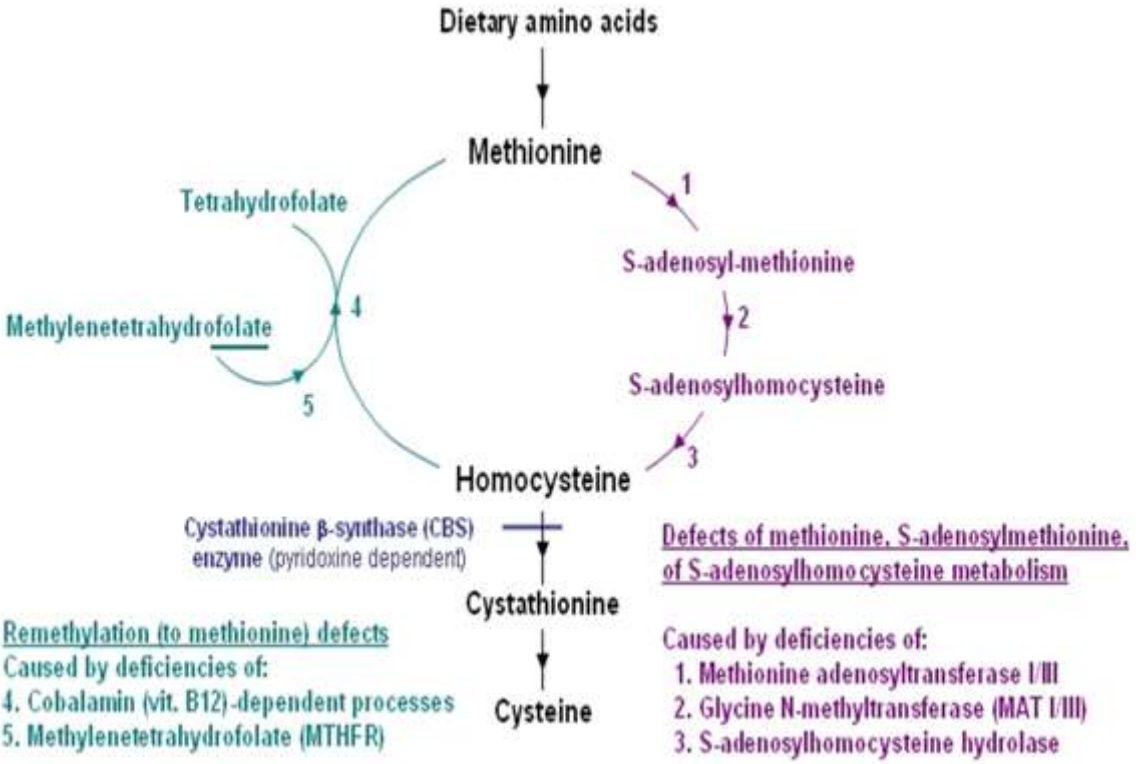

Figure 12: Metabolic pathways of homocysteine and their defects

Homocystinuria, due to cystathionine beta-synthase deficiency

It is an inherited autosomal recessive trait (Gene Map Locus: 21q22.3) characterized by an accumulation of homocysteine in the serum and an increased excretion of homocysteine in the urine. This defect leads to a multisystemic disorder of the connective tissue, muscles, CNS, and cardiovascular system.

Incidence

Studies have reported that 1 in every 250,000 people in the general population is affected by the disease, but this figure is widely believed to be too low. Several studies estimate the populations in particular countries and regions as follows: Ireland (1 in 65,000), Germany (1 in 17,800), Norway (1 in 6,400), and Qatar (1 in 3,000).

Clinical Signs and Symptoms

This defect leads to a multisystemic disorder of the connective tissue, muscles, CNS, and cardiovascular system. Thus, the symptoms developmental delay/intellectual disability, ectopia lentis (dislocation of the ocular lens) and/or

severe myopia, skeletal abnormalities such as excessive height and length of the limbs and vascular abnormalities characterized by thromboembolism

Diagnosis

Homocysteinemia can be tested by presence of:

- increased concentrations of plasma homocystine, total homocysteine, and methionine;
- increased concentration of urine homocystine
- reduced cystathionine β-synthase (CBS) enzyme activity.

Treatment and management

Treatment includes using vitamin B6 (pyridoxine) therapy, protein-restricted and methionine-restricted diets, betaine treatment, and/or folate and vitamin B12 supplementation. Betaine (N,N,N-trimethylglycine) is used to reduce the concentration of homocysteine by promoting the conversion of homocysteine to methionine.

Maple Syrup Urine Disease (MSUD)

It is a type of organic acidemias. It is also called branched chain ketoaciduria. It is due to build up of branched chain amino acids (L-leucine, isoleucine and valine) (Figure 13) and their toxic by-products in the blood and urine that make urine smell like maple syrup or burning sugar. It is due to branched-chain α-ketoacid dehydrogenase deficiency (Figure 14) and it is an autosomal recessive metabolic disorder (Figure 15). Infants, with the disease, seem healthy at birth but if left untreated suffer severe brain damage and eventually die (Figure 16).

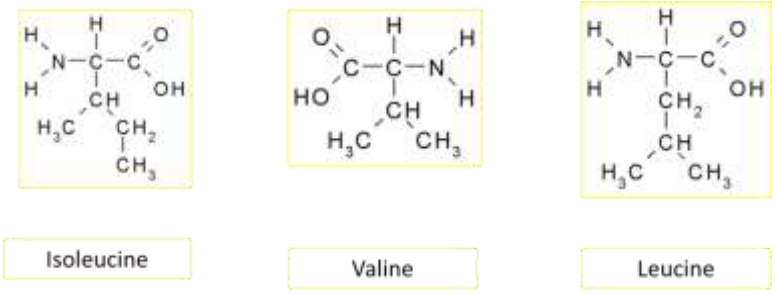

Figure 13: Branched Chain Amino Acids

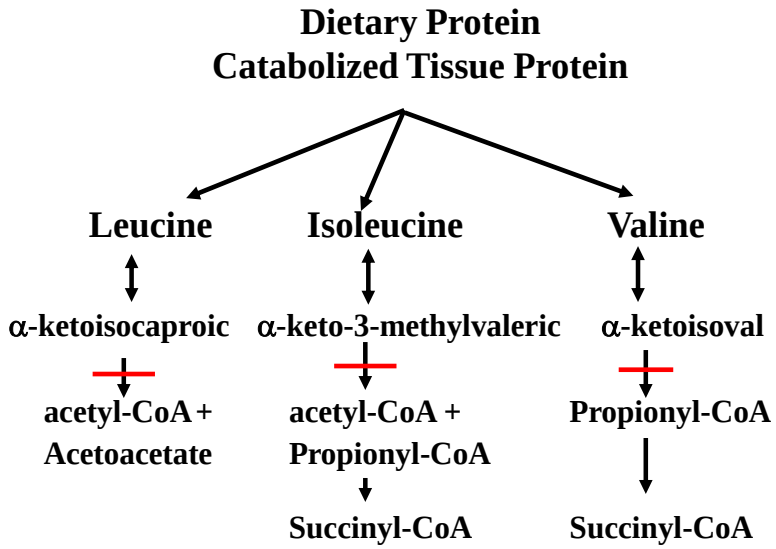

Figure 14: Branched-chain α-keto acid dehydrogenase deficiency

Catabolism

Catabolism of branched chain amino acids occurs through the steps:

- Transamination
- Oxidative Decarboxylation*
- Dehydrogenation
- End products

* Enzyme responsible: Branched-chain α-ketoacid dehydrogenase (Figure 14).

Branched-chain α-ketoacid dehydrogenase

It is a complex enzyme system using tyrosine pyrophosphate (Vit B1) as coenzyme. This mitochondrial enzyme consists of four subunits E1α, E1β, E2, E3. Deficiency of this enzyme causes Maple Syrup Urine Disease (MSUD).

Genetic defects

MSUD results from mutation in many genes; the most common are:

19q13.2: Mutation in the E1-alpha subunit gene is referred to as MSUD type IA (BCKDHA).

6q14.1: Mutation in the E1-beta subunit gene as type IB (BCKDHB).

1p21.2: Defect in the E2 subunit gene as type II (BCKDHC).

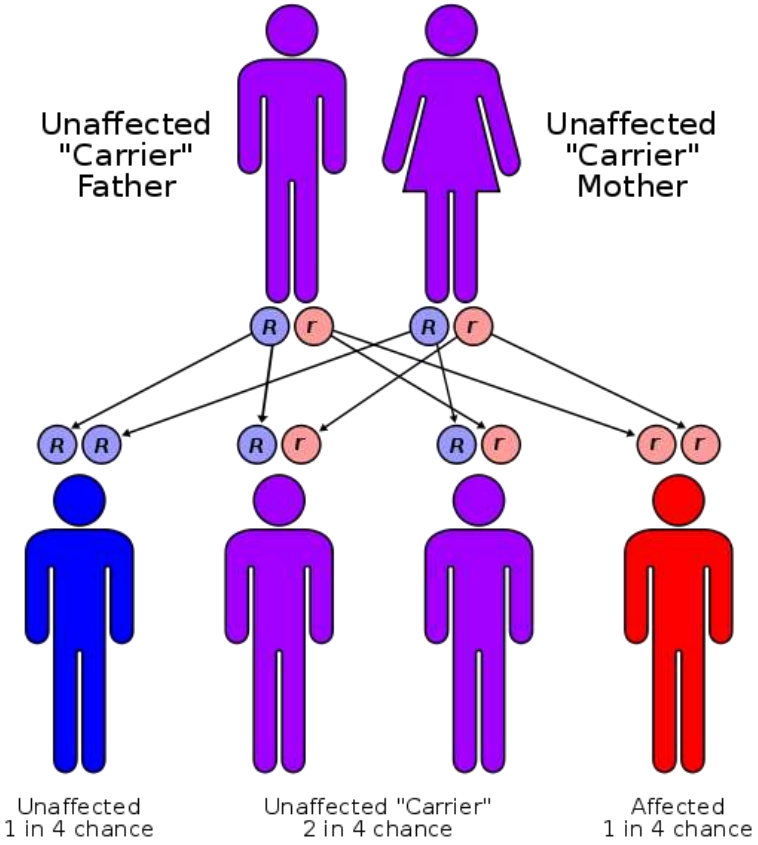

Figure 15: Inheritance of MSUD in neonates

Types

BCKDHA (chr 19) is responsible for expression of branched chain ketoacid dehydrogenase.

BCKDHB (chr 6)

MUSD 2, type II (chr 1)

MUSP3 (chr 7)

All work to create proteins for complex are and autosomal recessive (Figure 15).

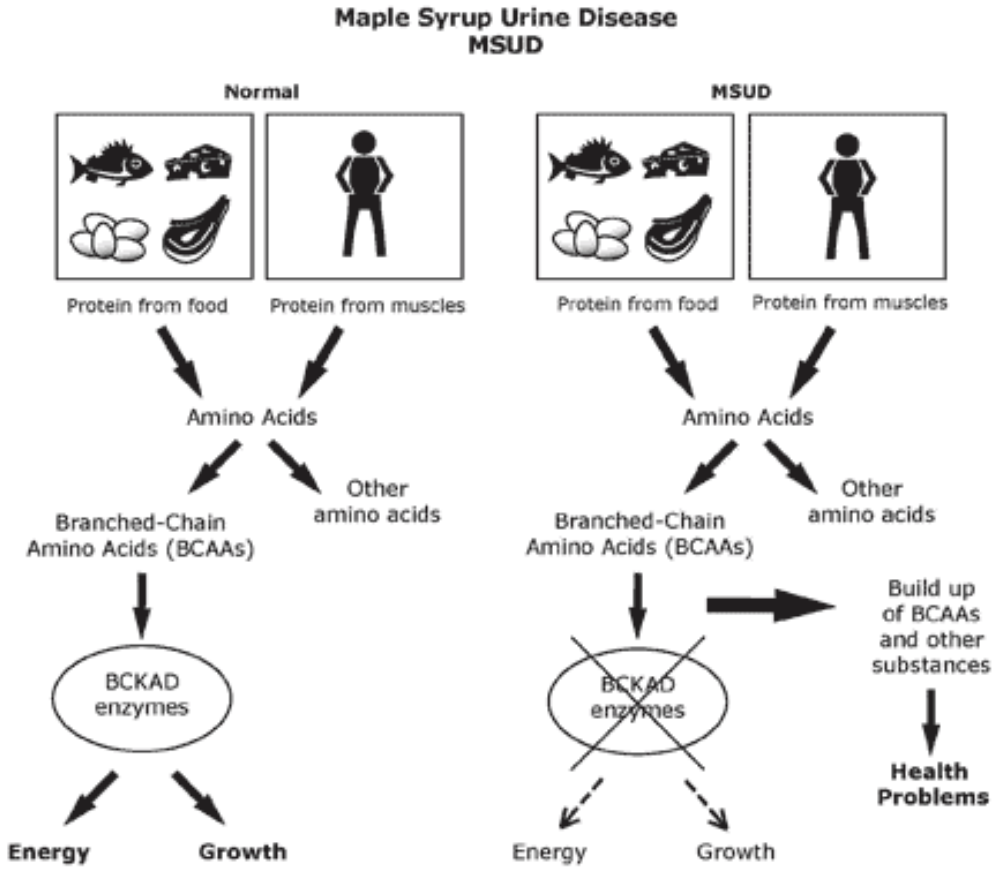

Figure 16: The effects of MSUD

5 phenotypes have been identified based on clinical findings and response to thiamine. These are:

1. Classic severe MSUD
2. Intermittent MSUD
3. Mild (Intermediate) MSUD
4. Thiamine-responsive MSUD
5. MSUD due to deficiency in E_3 subunit with lactic acidosis

The most common and severe form of the disease is the classic type, which appears soon after birth. Variant forms of disorder may appear later in infancy, but are typically less severe, but still involve mental and physical problems if untreated.

Treatment of Classic MSUD

- In acute phase:
  - Adequate hydration
  - Quick removal of metabolites via Peritoneal Dialysis
- After acute phase:
  - Diet low on branched chain amino acids
- Carnitine supply helps to excrete organic acids in the urine

Incidence of MSUD

Prevalence is 1 / 185,000. Classic form is more prevalent. MSUD has a much higher prevalence in children of Amish, Mennonite, and Jewish descent

Signs and symptoms of classic MSUD

The clinical manifestations include poor feeding, ketoacidosis, coma, vomiting, dehydration, lethargy, seizures, pancreatitis, hypotonia and hypoglycemia. If untreated, will lead to death, coma and neurological decline.

Diagnosis (Testing)

MSUD can be diagnosed by:

1) Sweet-smelling urine with an odor similar to that of maple syrup
2) Deficiency of branched chain alpha keto acid dehydrogenase
3) Elevation of levels of branched chain amino acids (leucine, isoleucine and valine) and their toxic by-product in serum and urine.

Treatment and management

Treatment and management can be performed as follows:

1) In acute phase, quick removal of metabolites via Peritoneal Dialysis.
2) After acute phase, diet with minimal levels of amino acids, leucine, isoleucine and valine to prevent neurological disorders.
3) Carnitine supply helps to excrete organic acids in the urine.

Glutaric acidemia type I

It is also known as aciduria I or GA I. It is an autosomal recessive metabolic disorder with gene map locus:19p13.2. It is due to glutaryl CoA dehydrogenase deficiency (Figure 17).

Glutaric acid is the core molecule of glutaryl-coenzyme A (glutaryl-CoA). Glutaryl-CoA is produced during the degradation of 3 amino acids - lysine, hydroxylysine and tryptophan. The defective enzyme, glutaryl-CoA dehydrogenase, prevents the further metabolism of glutaryl-CoA causing the excessive formation of glutaric acid which appears in the urine (glutaric aciduria) and in the blood (glutaric acidemia) (Figure 17). The formed glutaric acid can combine with carnitine to form glutaryl carnitine thus depleting the body's supply of carnitine. Carnitine is a substance that is essential for the oxidation of fatty acids so that the secondary deficiency of carnitine in glutaric aciduria can impair fat metabolism. Glutaric aciduria can be controlled and managed by feeding low protein diet to limit lysine and tryptophan intake, and carnitine supplement to replace the secondary deficiency.

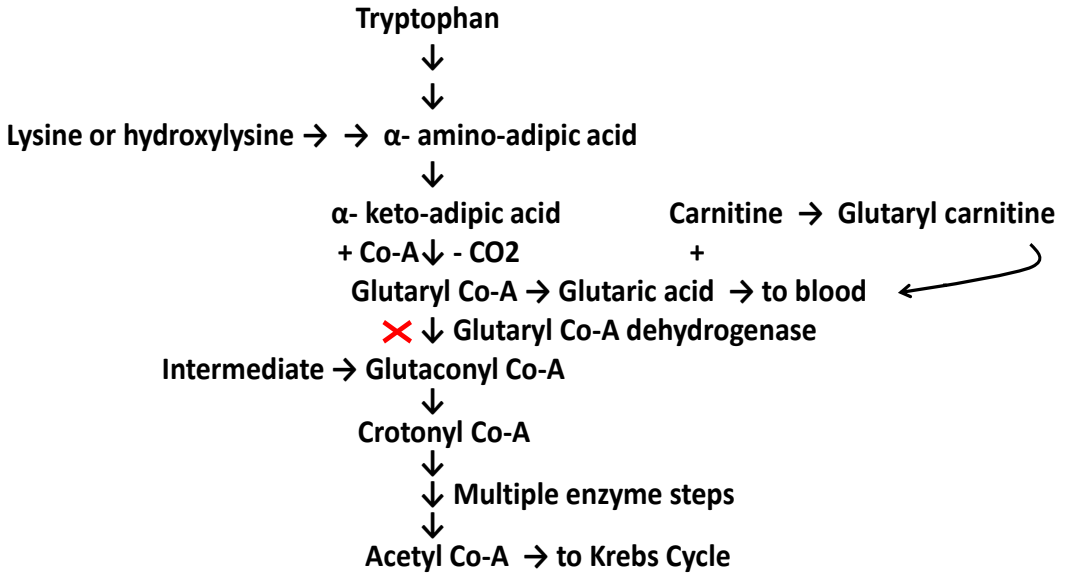

Figure 17: In various cells, the amino acids lysine, tryptophan, and hydroxylysine are broken down in separate pathways that all meet at glutaryl CoA. Glutaryl-CoA is then processed to form acetyl-CoA that produces energy in those cells. In glutaric aciduria (right), defective glutaryl-CoA dehydrogenase prevents glutaryl-CoA metabolism (X). Instead glutaric acid accumulates and carnitine becomes depletedsecondarily because it combines with glutaric acid to form glutaryl carnitine.

Symptoms and Syndromes

- Babies with glutaric acidemia type 1 often are born with unusually large heads (macrocephaly).
- There are also spasms, jerking, rigidity or decreased muscle tone and muscle weakness
- Some individuals with glutaric acidemia have developed bleeding in the brain or eyes.

Diagnosis

The presence of glutaric acidemia or aciduria type I can be detected by:

1) high levels of glutaric acid and glutaryl carnitine in the blood.
2) the urinary excretion of glutarylcarnitine and glutaric acid.
3) Deficiency of glutaryl Co-A dehydrogenase in tissues.

Incidence

Glutaric acidemia type I occurs in about 1 in 100,000 infants worldwide

Treatment and management

The GA I can be managed and treated by supplementation of

1) Diet restricted in lysine, hydroxylysine and tryptophan.
2) Carnitine
3) Vegetarian diets and, for younger children, breastfeeding are common ways to limit protein intake without endangering tryptophan transport to the brain.

Hyperammonemia and defects in ornithine cycle (urea cycle)

Ammonia and urea cycle

Ammonia is produced by deamination of amino acids to form keto acids. Ammonia is a very toxic substance. It is converted to the less toxic substance urea prior to excretion in urine by the kidneys (Figure 18). The metabolic pathways that synthesize urea are located first in the mitochondria and then into the cytosol (cytoplasm). The

process is known as the urea cycle or ornithine cycle, which comprises several enzymes acting in sequence (Figure 19).

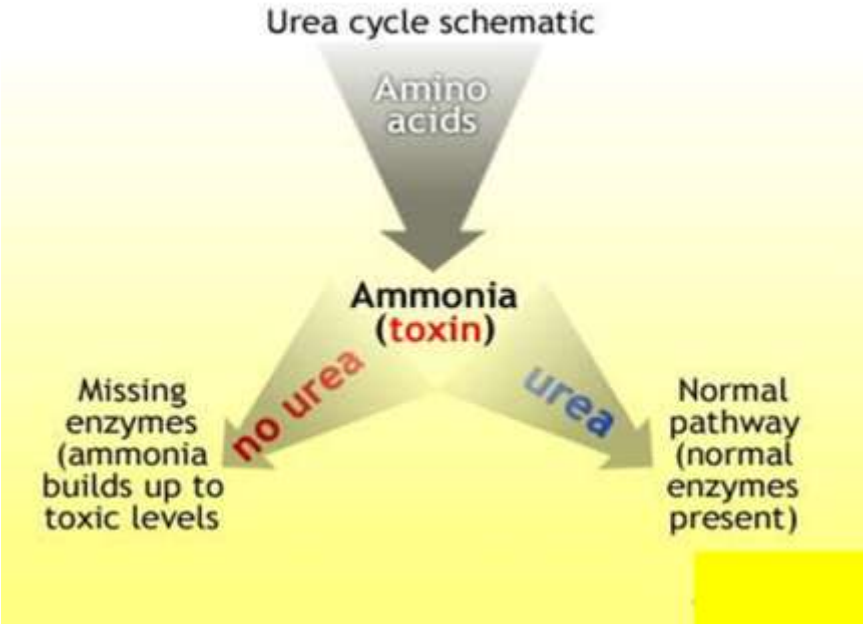

Figure 18: Conversion of ammonia to urea

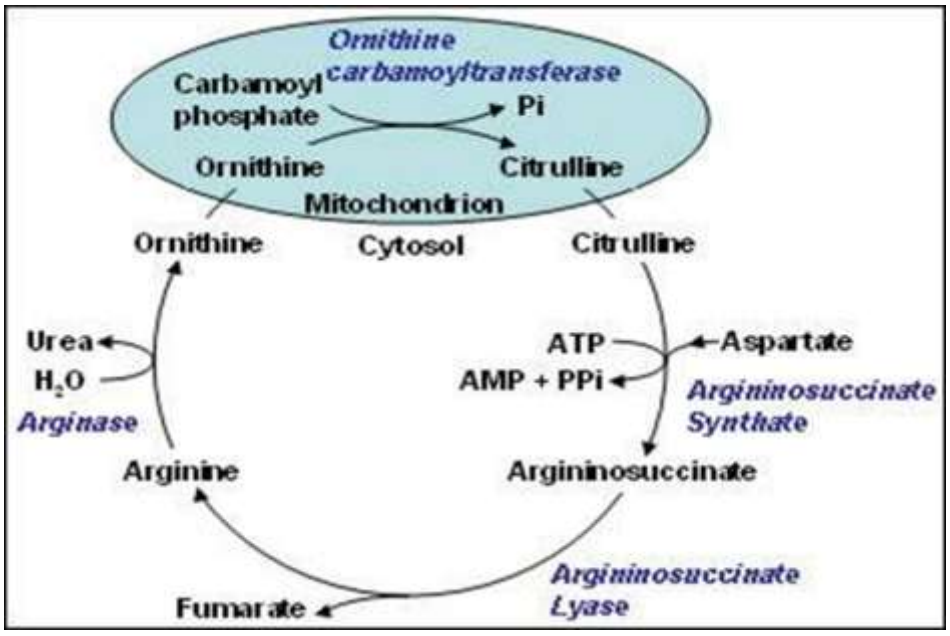

Figure 19: Five disorders of hyperammonemia involving different defects in the biosynthesis of the enzymes of the urea cycle have been described: carbamyl phosphate synthetase deficiency, OTC deficiency, argininosuccinate synthetase deficiency, or citrullinemia, argininosuccinate lyase deficiency, and arginase deficiency.

Hyperammonemia without metabolic acidosis usually have respiratory alkalosis. Urea cycle disorders include **ornithine transcarbamylase deficiency (X-linked disorder), carbamoyl phosphate synthase deficiency (Autosomal recessive; AR), citrullinemia (AR), argininosuccinic acidemia (AR)** and **argininemia (AR) (**Figure 19**).**

Hyperammonemia

Hyperammonemia (or hyperammonaemia) is a metabolic disturbance characterised by an excess of ammonia in the blood. It is a dangerous condition that may lead to encephalopathy and death. It may be primary or secondary.

Primary vs. secondary

- Primary hyperammonemia is caused by several inborn errors of metabolism that are characterized by reduced activity of any of the enzymes in the urea cycle.
- Secondary hyperammonemia is caused by inborn errors of intermediary metabolism characterized by reduced activity in enzymes that are not part of the urea cycle (e.g. Propionic acidemia, Methylmalonic acidemia) or dysfunction of cells that make major contributions to metabolism (e.g. hepatic failure).

Specific types

The following list includes such examples:

1) hyperammonemia due to ornithine transcarbamylase deficiency (OTC; it is the most common type of primary hyperammonemia.
2) hyperinsulinism-hyperammonemia syndrome (glutamate dehydrogenase 1)
3) hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (ornithine translocase)
4) hyperammonemia due to N-acetylglutamate synthetase deficiency

5) hyperammonemia due to carbamoyl phosphate synthetase I deficiency (carbamoyl phosphate synthetase I)
6) hyperlysinuria with hyperammonemia (genetics unknown)
7) Methylmalonic acidemia
8) Isovaleric acidemia
9) Propionic acidemia
10) Carnitine palmitoyltransferase II deficiency
11) Transient hyperammonemia of the newborn, specifically in the preterm.

Hyperammonemia due to deficiency of OTC

Hyperammonemia due to deficiency of OTC is X-linked inborn error of metabolism (gene map locus: Xp11.4). It is characterized by increased tissues and blood ammonia.

Signs and symptoms

The clinical features include:

1) Ammonia intoxication,
2) mental deterioration,
3) Hyperammonemic comas and
4) Ecephalopathy and death.

Incidence

OTC deficiency has a frequency of 1 in 80,000 births in Japan. The total frequency of this and the other urea cycle enzymopathies, carbamoyl phosphate synthetase deficiency, argininosuccinate synthetase deficiency, argininosuccinate lyase deficiency, and arginase deficiency, in Japan was 1 in 46,000.

Diagnosis (Testing)

The hyperammonemia due to OTC deficiency

1) Detection of OTC in liver biopsies.
2) Increased ammonia levels in serum and urine.

Treatment and management

Hyperammonemia can be controlled and managed through three directions:

A) <u>Diet</u>:

1) a very low protein diet

2) Caloric intake is provided by glucose and fat.

B) <u>Drugs:</u>

Treatment with sodium phenyl acetate and sodium benzoate.

1) Sodium phenyl acetate conjugates with glutamine to form phenyl acetyl glutamine which is excreted by the kidney

2) Sodium benzoate conjugates with glycine to form hippuric acid which is rapidly excreted by the kidneys.

A preparation containing sodium phenyl acetate and sodium benzoate is available under trade name Ammonul.

C) <u>Peritoneal dialysis or hemodialysis</u> to remove ammonia.

Disorders of fatty acid oxidation and mitochondrial metabolism

Fatty acid oxidation and its disorder

Fatty acids are oxidized by very long chain, long chain, medium chain and short chain acyl CoA dehydrogenases to form acetyl CoA or propionyl CoA and acetyl CoA that enters Krebs cycle to produce energy (Figure 20). The number of acetyl CoA produced from fatty acid oxidation exceeds the capacity of Krebs cycle. Thus, each 2 of the excess acetyl CoA molecules combine to form acetoacetic acid that can be decarboxylated to aceton or reduced (hydrogenated) to form β-hydroxy butyric acid. Acetoacetic acid, aceton and β-hydroxy butyric acid are keton bodies and their accumulation in blood is known as ketonemia and their excretion in urine is called ketonuria. Distinguishing feature of fatty acid oxidation disorder (FAOD) in fasting is *hypoketotic hypoglycemia*. Medium chain acyl CoA dehydrogenase deficiency (MCAD) is most common and has a 25% risk of death with first episode. LCAD (Long chain acyl CoA dehydrogenase), VLCAD (very long chain acyl CoA dehydrogenase) and carnitine uptake disorder are variably associated with, hepatomegaly, liver disease, hypertrophic cardiomyopathy and potential arrhythmias. All are autosomal recessive. Carnitine is essential for entrance of acyl CoA in mitochondria for further oxidation (Figure 21).

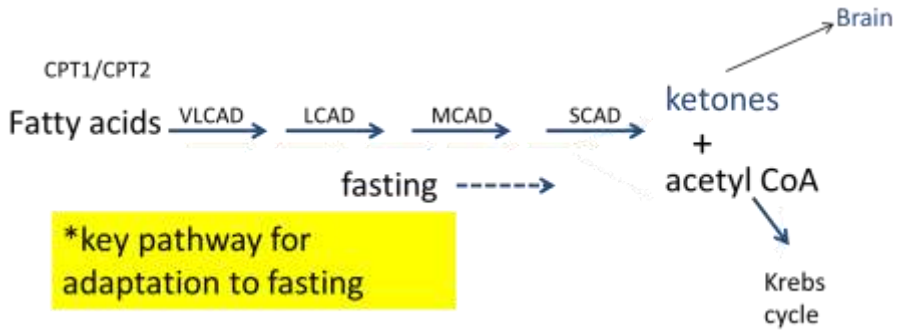

Figure 20: Fatty acid oxidation and key pathway for adaptation to fasting.

Carnitine palmitoyltransferase I and II (CPT 1 and 2); VLCAD, LCAD, MCAD and SCAD are very long chain, long chain, medium chain and short chain acyl CoA dehydrogenases respectively.

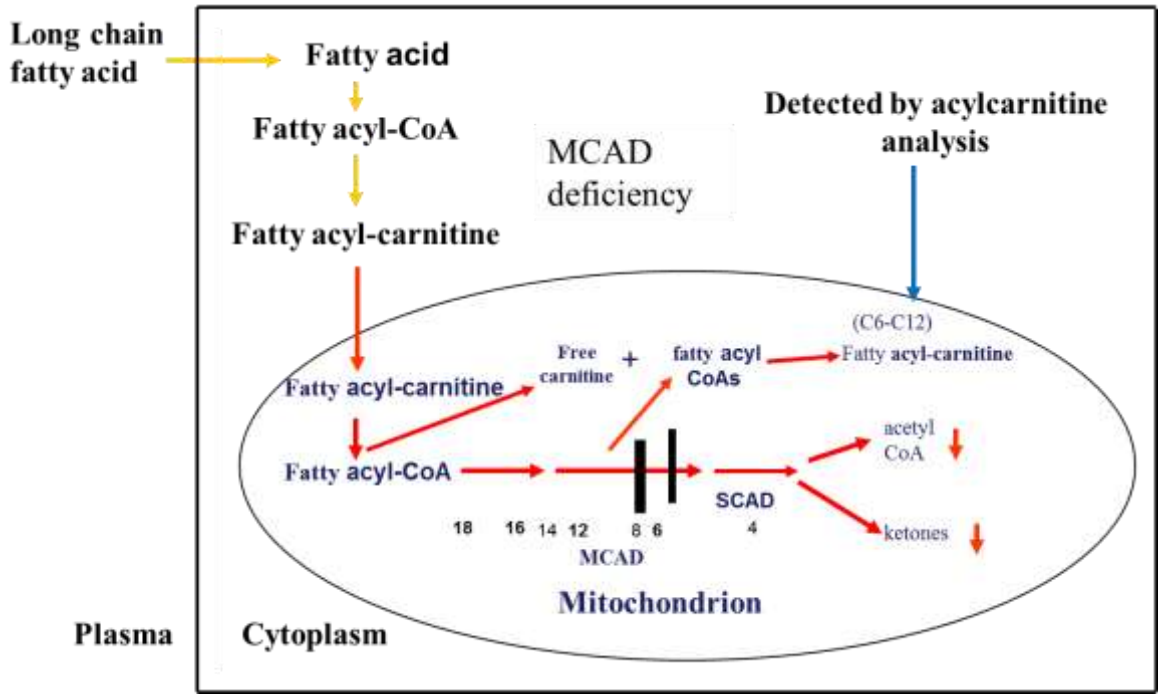

Figure 21: Diagnosis of fatty acid oxidation disorders by acylcarnitine analysis

Variable Clinical presentations of fatty acid oxidation

1) Hyoketotic hypoglycemia in neonatal period
2) Later onset hypoketotic hypoglycemia
3) Sudden infant death syndrome
4) Hypotonia (Low muscle tone).
5) Failure to thrive (to indicate insufficient weight gain or inappropriate weight loss).
6) Hypertrophic cardiomyopathy, arrythmias
7) Liver disease
8) Adolescent or adult onset myopathy
9) Asymptomatic

In addition, clinical presentations of different types of fatty acid oxidation disorders (VLCAD, LCAD, MCAD and SCAD) are shown in table 1.

Table 1: Fatty acid oxidation disorders

Disease	Typical presentation	Comments
SCAD	Probably benign	N/A
MCAD	Hypoketotic hypoglycemia	Most common FAOD, may be associated with "SIDS; Sudden Infant Death Syndrome (SIDS)"
VLCAD	Variable: hypoketotic hypoglycemia, hypertrophic cardiomyopathy, myopathy, hepatopathy	Extemely variable ranging from neonatal to adult onset
LCHAD	Variable: hypoketotic hypoglycemia, hypertrophic cardiomyopathy, myopathy, hepatopathy.	Extremely variable, need low fat diet

Diagnosis is based on the specific pattern of acylcarnitine elevations

Disorders of carnitine metabolism

(1)Carnitine transports long chain fatty acids into the mitochondria
(2)Carnitine deficiency can be primary or secondary
(3)Primary carnitine deficiency is caused by abnormal transport of carnitine itself into the cells (carnitine uptake disorder, AKA "systemic carnitine deficiency")
(4) Secondary carnitine deficiency is caused by other metabolic disorders through the formation of carnitine esters (acylcarnitines) by abnormal organic/fatty acids

Primary (CUD)

Plasma:
- **Decreased total carnitine**
- **Decreased free carnitine**
- **Normal acyl/free ratio**

Urine:
- **Normal total carnitine**
- **Normal or increased free carnitine**
- **Normal acyl/free ratio**

MCAD, organic acidemias etc

Plasma:
- **Decreased/normal total carnitine**
- **Decreased free carnitine**
- **Increased acyl/free ratio**

Urine:
- **Decreased/normal total carnitine**
- **Decreased free carnitine**
- **Increased acyl/free ratio**

Glutaric Aciduria type II
as
a fatty acid oxidation defect

Glutaric aciduria II (GA II) is an autosomal recessively inherited disorder of fatty acid, amino acid, and choline metabolism. It differs from GA I in that multiple acyl-CoA dehydrogenase deficiencies result in large excretion not only of glutaric acid, but also of ethylmalonic, butyric, isobutyric, 2-methyl-butyric, and isovaleric acids (Figure 22). GA II results from deficiency of any 1 of 3 molecules: the alpha (ETFA) and beta (ETFB) subunits of electron transfer flavoprotein, and electron transfer flavoprotein dehydrogenase (ETFDH).

The clinical picture of GA II due to the different defects appears to be indistinguishable; each defect can lead to a range of mild or severe cases, depending presumably on the location and nature of the intragenic lesion, i.e., mutation, in each case.

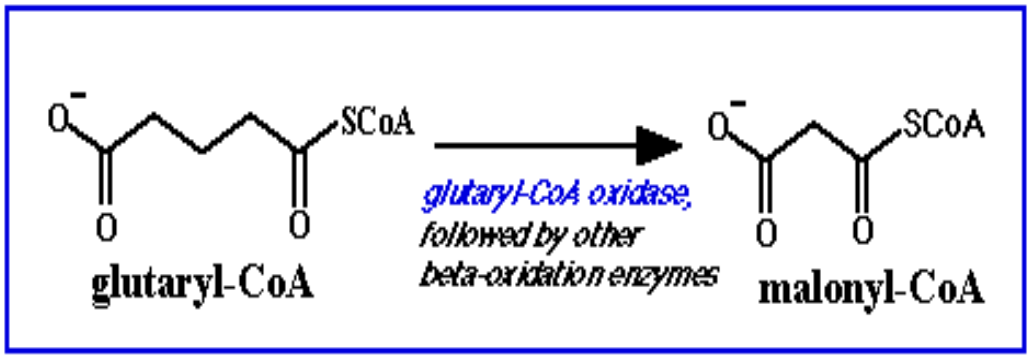

Figure 22: Multiple acyl-CoA dehydrogenase deficiencies subsequent to this reaction in glutaric aciduria type II

Glutaric acid is an intermediate in three major metabolic pathways:

- Fatty acid metabolism
- Lysine metabolism
- Tryptophan metabolism

Fatty acid oxidation defects may be due to

- Short chain acyl-CoA dehydrogenase def. (SCAD)
- Medium chain acyl-CoA dehydrogenase def. (MCAD)
- Long chain acyl-CoA dehydrogenase def. (LCAD)
- Multiple acyl-CoA dehydrogenase def. (MAD)
- Riboflavin responsive defects of ß-oxidation (RR-MAD)
- 3-Hydroxy-3-methylgtutaryl CoA (HMG-CoA) lyase def.

MAD deficiencies

Defects in electron transfer flavoprotein (ETF) & its dehydrogenase (ETF-DH) impairs transfer of electrons into mitochondria electron transfer chain.

- There are 2 types which are:
  1. (MAD-S) severe neonatal form or.
     Glutaric acidemia type II.
  2. (MAD- M) mild "late onset" variant.
     ethyl-malonic-adipic aciduria.

According to the genetic and phenotypic traits, there are three types that are represented in table 2.

Table 2: Gene Map Locus of glutaric aciduria II

Location	Phenotype	Gene mutations
4q32.1	Glutaric acidemia IIC	mutations in the ETFDH gene
15q24.2-q24.3	Glutaric acidemia IIA	mutations in the ETFA gen
19q13.41	Glutaric acidemia IIB	mutations in the ETFB gene

Glutaric aciduria II (MAD-*S*)

It is severe neonatal form and it has clinical and metabolic manifestations that include acidosis, hypoglycemia, coma, hypotonia (low muscle tone; reduced muscle strength and muscle weakness) & cardiomyopathies.

- This type of MAD-S is classified into two subgroups
    1. With congenital anomalies.
    2. Without congenital anomalies.

Clinical signs and symptoms includes

- Growth retardation.
- Special odor.
- Metabolic acidosis.
- Hypoglycemia.
- Dysmorphism.
- Early neonatal death.
- Def of electron transport chain flavoprotein or its oxidoreductase.
- Abnormal liver (including function)
- Biliary atresia & stenosis
- Macrocephaly
- Large kidneys & Multiple renal cysts
- Organic aciduria
- Pancreas (exocrine), general abnormalities
- Undermineralization of skull
- Brain, general abnormalities.
- Club foot/hindfoot, varus (Figure 23).
- Rocker-bottom feet / hindfeet (Figure 23).

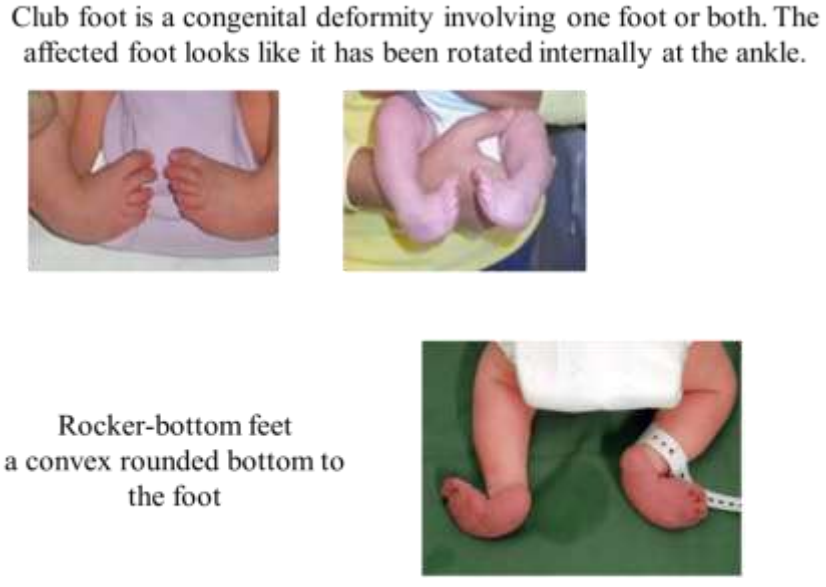

Figure 23: Club feet and Rocker-bottom feet

Diagnosis

- Urinary organic acid profile.

Shows ↑- Ethyl-malonic acid

- ethylmalonic, butyric, isobutyric, 2-methyl-butyric, and isovaleric acids
- Lysine

- Blood metabolic screening :

Shows ↑- Glutaric acid

- ethylmalonic, butyric, isobutyric, 2-methyl-butyric, and isovaleric acids
- Lysine

Differentiate from GA type I.

- Def. Of glutaryl CoA dehydrogenase.
- Progressive dystonia & dyskinesia.
- Vomiting , seizures, coma.
- Ketosis, hypoglycemia, hyperammonemia & hepatitis picture.
- High conc of glutaric acid in serum & urine.
- ↑ 3- Hydroxyglutaric acid.

  C.F. ↑2- Hydroxyglutaric acid in GA II.

N.B. Glutaric aciduria type III is a peroxisomal disorder. Very long chain fatty acids

Treatment and management

- Acute illnesses:
  1. Prompt treatment with glucose solution D10% to suppress lipolysis.
  2. Correct acidosis.
- Chronic:
  1. Avoid starvation.
  2. Special formula. (low protein-low fat).
  3. Carnitine & riboflavin supplements.

Table 3: Selected Organic Acidemias

Disease	Cofactor	Other features	Wide anion gap ketoacidosis
Propionic	biotin	Usually severe	+
Methylmalonic	B12	Some respond to B12	+
Isovaleric	riboflavin	Sweaty foot odor to urine	+
Glutaric	riboflavin	Macrocephaly, dystonia, Abnormal MRI	+
Maple syrup urine	thiamine	Maple syrup odor, elevated branched chain amino acids	+

Table 4: Urea cycle disease versus organic acidemias

	UCD	OA
lethargy/coma	+	+
vomiting	+	+
hyperammonemia	+ +	+/-
metabolic ketoacidosis	-	+
primary respiratory alkalosis	+	-

Inherited hyperbilirubinemias and Disorders of bilirubin conjugation

Bilirubin was formed from hemoglobin by oxidative cleavage of a porphyrin in heme, which affords biliverdin. Biliverdin is reduced to bilirubin (Figure 24). After conjugatation with glucuronic acid to form bilirubin mono and diglucuronides by the enzyme UDP-glucuronyltransferase, conjugated bilirubin is released into bile (Figures 25, 26 and 27). Bilirubin derives from two main sources. The majority (80%) of the bilirubin formed in the body comes from the heme released from senescent red blood cells. The remainder originates from various heme-containing proteins found in other tissues, notably the liver and muscles. The excreted conjugated bilirubin is converted by bacterial proteases in the intestine into urobilinogen which can be oxidized to form urobilin and stercobilin (giving stool and urine their characteristic colors). Most of urobilingen (more than 90%) was excreted in faeces and less than 10% is reabsorbed by enterohepatic circulation to be excreted by the kidney (Figure 27).

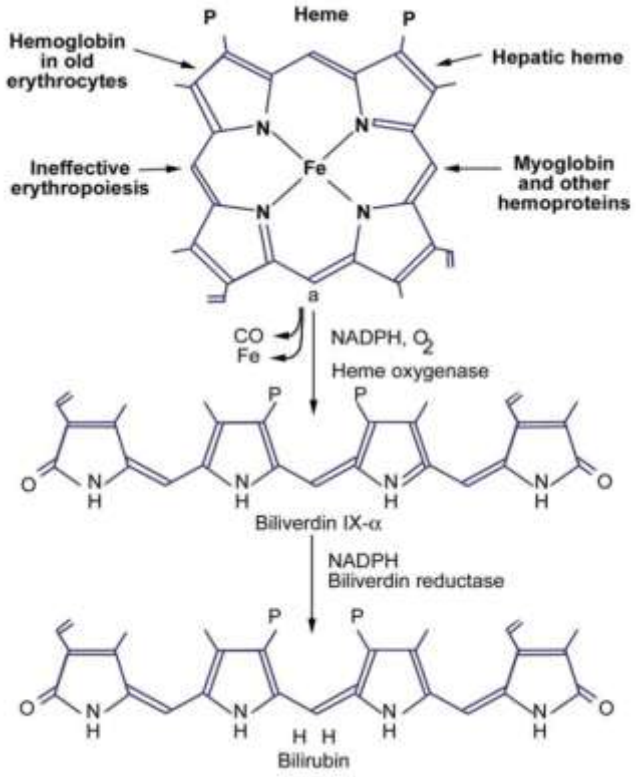

Figure 24: Formation of bilirubin and biliverdin from heme.

https://emedicine.medscape.com/article/178841-overview

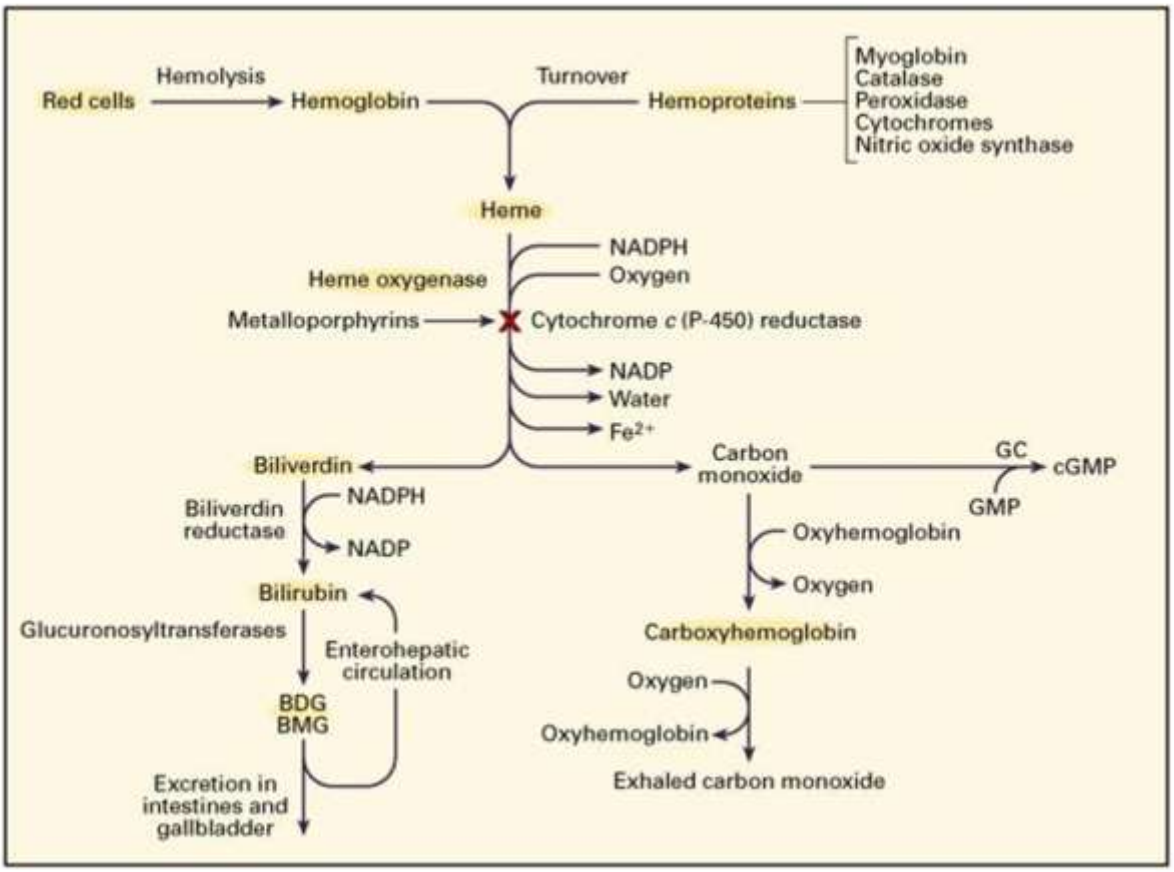

Figure 25: Formation and Metabolism of bilirubin. Lowe A. 2015. The Liver Bilirubin Metabolism. Stanford University.

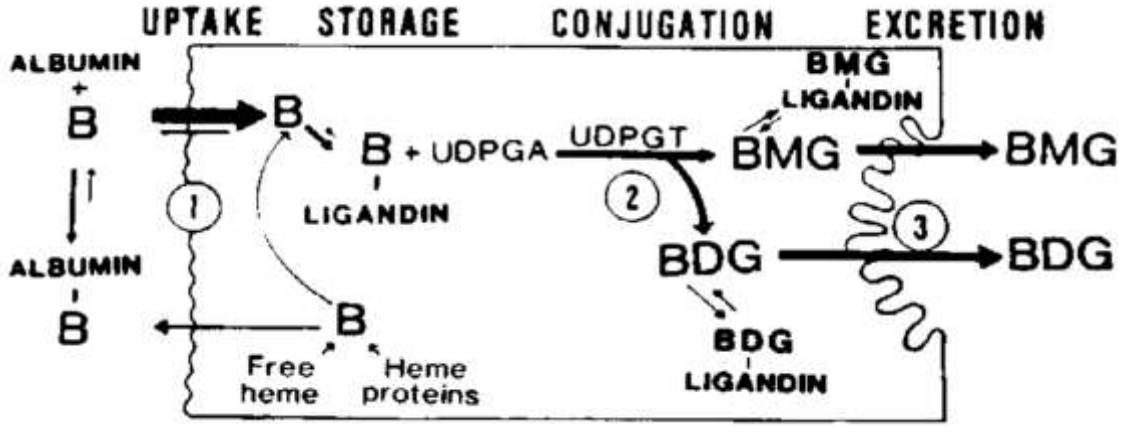

Figure 26: Uptake, storage, conjugation and excretion of bilirubin. Lowe A. 2015. The Liver Bilirubin Metabolism. Stanford University.

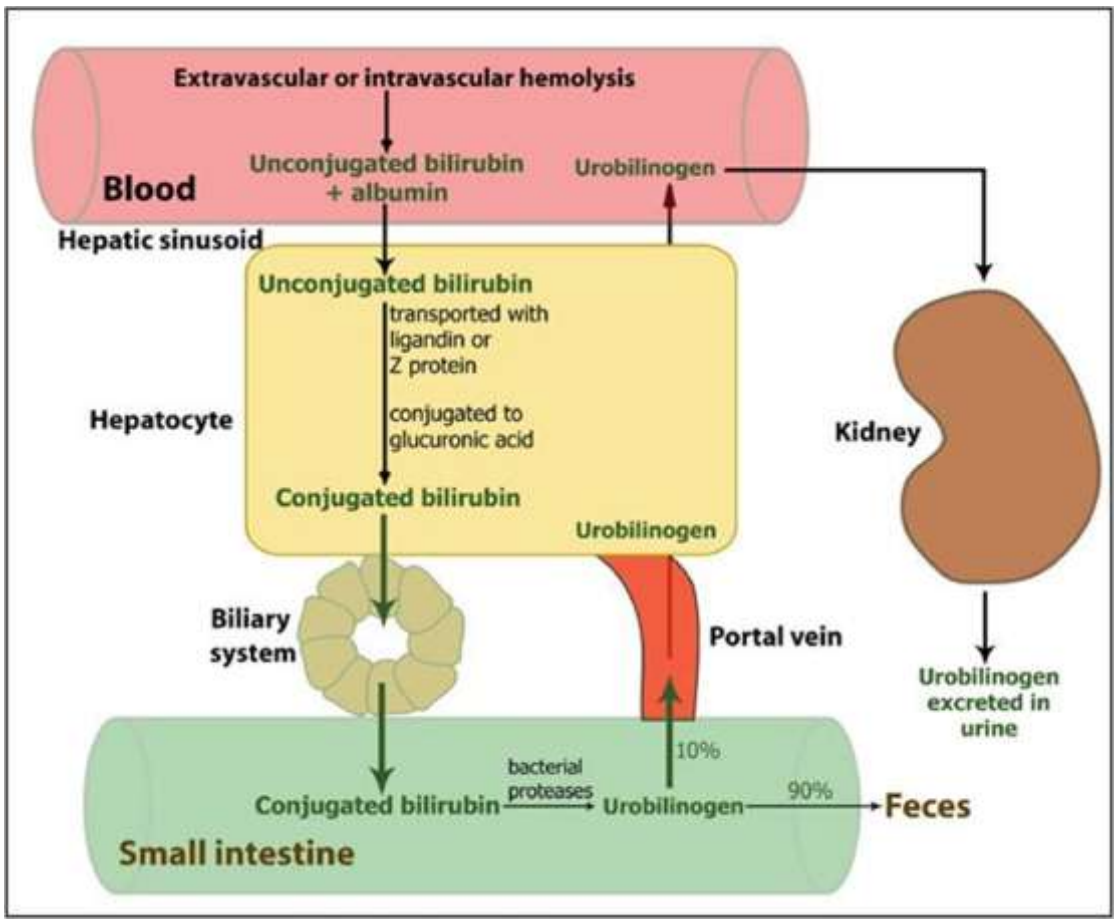

Figure 27: Bilirubin conjugation and excretion. Lowe A. 2015. The Liver Bilirubin Metabolism. Stanford University.
http://www.eclinpath.com/chemistry/liver/cholestasis/bilirubin/

The hyperbilirubinemia may be due to elevated plasma levels of indirect (unconjugated) bilirubin or direct (conjugated) bilirubin.

The occurrence of an unconjugated (indirect) hyperbilirubinemia may be due to

(1) over production of bilirubin as a result of increased hemolysis,

(2) decreased hepatic uptake or conjugation or both

(3) genetic defect of UDP-glucuronyltransferase

In viral hepatitis, hepatocellular damage, toxic or ischemic liver injury, higher levels of serum conjugated bilirubin is seen.

Direct (conjugated) hyperbilirubinemia may result from a mechanical blockage in the duct system that can occur from a gallstone or malignancy or portal inflammatory cell infiltration.

There are four inherited types of hyperbilirubinemia. These include

- Crigle-Najjar syndrome
- Gilbert syndrome
- Dubin-Johnson syndrome
- Rotor syndrome

Crigle-Najjar Syndrome

- It is autosomal recessive.
- Its gene map locus is 2q37.1
- It results from mutation in the UDP-glycuronyltransferase gene.
- Two types of Crigler-Najjar syndrome are defined.

  1- Crigle-Najjar syndrome type 1: Infants have complete absence of bilirubin UDP-glucuronyltransferase (UDPGT)

  2- Crigle-Najjar syndrome type 2: Infants have a partial deficiency of this enzyme, are less severely jaundiced and have pigmented bile

Crigle-Najjar Syndrome Type 1

It is super-rare and it is autosomal recessive disorder. The patients of this disorder have no UGT1A1 activity. UGT1A1 is a liver enzyme that participates in bilirubin processing (it conjugates bilirubin with one or two molecules of glucuronic acid). The bile is colorless, with only trace amounts of unconjugated bilirubin. The unconjugated bilirubin backs up into the blood, producing severe jaundice and icterus. The liver, by the way, looks totally normal under the microscope. Crigle-Najjar type 1 is fatal in the neonatal period unless the baby gets a liver transplant.

Crigle-Najjar Syndrome Type II

It is an autosomal dominant disorder. Patients have decreased UGT1A1 activity (the enzyme is only capable of forming monoglucuronidated bilirubin). The disorder is not fatal. In fact, the major consequence is simply really yellow skin.

Diagnosis

Diagnosis to differentiate between Crigle-Najjar syndrome type 1 and type 2 can be done by:

- Detection of conjugated bilirubin and unconjugated bilirubin
- Detection bilirubin-UDP-glucuronosyl transferase in liver biopsy

Bilirubin-UDP-glucuronosyltransferase is completely absent in Crigler-Najjar syndrome type I.

Crigler-Najjar syndrome type 1 patients do not respond to phenobarbital treatment but type II patients respond.

Clinical Features, Signs and Symptoms

- Nonhemolytic jaundice with kernicterus
- Mental slowing, motor impairment, and seizures
- Bilirubin neurotoxicity in newborns and infants in **Crigler-Najjar syndrome type I**
- Brain damage and injury to basal ganglia, cerebellar, and likely hippocampal structures occur in **Crigler-Najjar syndrome type I**
- Bilirubin encephalopathy, hypotonia, deafness, oculomotor palsy and lethargy in **Crigler-Najjar syndrome type I**
- Intellectual impairment in **Crigler-Najjar syndrome type I**
- An abnormal EEG specially in **Crigler-Najjar syndrome type I**
- In **Crigler-Najjar syndrome type I**, intense jaundice appears in the first days of life and persists thereafter. Some affected infants die in the first weeks or months of life with kernicterus. Others survive with little or no neurologic defect.
- In **Crigler-Najjar syndrome type II**, patients have a partial deficiency of this enzyme, are less severely jaundiced, have pigmented bile that contains bilirubin glucuronide, and generally survive into adulthood without neurologic or intellectual impairment, although bilirubin encephalopathy may develop in later life.

Management and therapy

- Liver transplantation in Crigler-Najjar syndrome type I.
- Response to phenobarbital only in Crigler-Najjar syndrome type II is the most useful differential point.
- Before transplantation, the serum bilirubin level of Crigler-Najjar syndrome type I patients should be kept with daily phototherapy (Phototherapy is the use of visible light for the treatment of hyperbilirubinemia in the newborn). This relatively common therapy lowers the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver. Oral calcium supplementation makes phototherapy more efficient.
- Heme oxygenase inhibitors to reduce transient worsening of hyperbilirubinemia.
- Gene therapy in Crigler-Najjar syndrome type I.

Gilbert syndrome

This syndrome is common – it's estimated that 5-10% of the population has it. In this disorder, patients have a decreased activity of UGT1A1 (like Type II Crigle-Najjar). However, Gilbert syndrome (which is an autosomal recessive syndrome) has a UGT1A1 activity level of about 30% of normal, which is quite a bit higher than the amount of activity you see in CN. Patients usually have only mild hyperbilirubinemia (unconjugated, of course). There is no clinical consequence (other than an increased sensitivity to drugs that are metabolized by UGT1A1). Skin may turn yellow.

Dubin-Johnson syndrome

It is an autosomal recessive disorder. Patients have an increase in conjugated bilirubin in the blood. It is caused by a defect in secretion of bilirubin glucuronides (already conjugated) across the canalicular membrane (patients are missing a canalicular protein that transports bilirubin glucuronides into bile). The liver looks normal in this disorder but it is darkly pigmented because of coarse granules within the hepatocyte cytoplasm. Most patients are asymptomatic (other than some jaundice here and there).

Rotor syndrome

It is an autosomal recessive disorder. The patients have an increase in conjugated bilirubin in the blood. The exact molecular defect is unknown – but it seems these patients have multiple defects in hepatocyte uptake and excretion of bilirubin pigments. The liver looks normal, and as in Dubin-Johnson syndrome. Most patients are asymptomatic (other than some jaundice).

Is the difference between Gilbert syndrome and Crigler-Najjar syndrome only in a degree of UGT deficiency?

- Gilbert Syndrome (like Crigler-Najjar syndrome type 2) is mild and causes no harm while Crigler-Najjar syndrome type 1 is a severe form and begins early in newborns.
- Gilbert Syndrome has clinical feature like Crigler-Najjar syndrome type 2 [both can be treated by barbiturates]
- Gilbert Syndrome (like Crigler-Najjar syndrome type 2) is usually asymptomatic.
- UDP glucuronosyltransferase 1-A1 (UGT) is absent Crigler-Najjar syndrome type 1 and is partially decreased in Crigler-Najjar syndrome type 2 and Gilbert syndrome
- Excretion problem in Dubin Johnson syndrome- Liver does not excrete bilirubin. So, conjugated bilirubin increases.
- Clinical manifestation is not the same as patients since Crigler-Najjar syndrome type 2 and Gilbert syndrome can lead to normal life whereas those with Crigler-Najjar syndrome type 1 usually die earlier (neonatal period); however both will give rise to unconjugated hypebilirubinemia.

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Case studies

Case study 1:

A six year old Malay boy was referred to Hospital University Sains Malaysia (HUSM) in January 1988 with the problem of aggressive behaviour and developmental delay. He was born in Mecca, Saudi Arabia after an uneventful pregnancy. His mother noticed at the age of three months that her child was rather quiet and could not hold his head up. He rolled over at eight months, sat without support at twenty months, walked at two years and talked with meaning at three years of age. At about one year old the mother noticed that his normal black hair gradually changed to light brown. There was no history of light hair on both parental sides. The child also had no history of fits or skin rashes. The parents were first cousins and one of the maternal grandfathers was mentally retarded. All their relatives were ethnic Malays. Clinical examination revealed a stunted child with height and weight below the 3rd centile and with light brown hair. He was very playful, hyperactive and shouted whenever he wanted something. He was very destructive and aggressive towards other children. He could not follow simple instructions and was unable to read, write alphabetical letters or even perform simple arithmatics. The gross motor development was normal. Using the Seguin Form Board Test his mental age was assessed to be below 3.5 years old. Apart from mental retardation the neurological examination was normal. There was no evidence of eczema and rest of physical examination was normal. Investigations revealed normal blood counts, blood glucose and electrolytes. The urine ferric chloride test was positive (blue-green) and dinitro-phenyl hydrazine test (ANPH) was also positive. The cyanide nitroprusside test was negative. Urine amino-acid thin layer chromatography (T.L.C) revealed a band of increased staining intensity which corresponded to the chromatogram of phenylalanine. Plasma amino-acid chromatography (T.L.C) revealed the phenylalanine band was increased. These two tests were repeated in March 1988 with similar conclusions. The other siblings and the parents were screened but did not reveal any abnormality: Electroencephalogram and computerized tomography of the brain were normal. In the management of this child, it was decided to embark on a low phenylalanine diet despite the late presentation for it was believed this diet could

improve behavior although not alleviate the mental retardation. The child was maintained on this diet with the help of the dietician and community health workers for almost six months. However, the child could not co-operate because of the unpalatability and the parents though helpful could not afford the cost of the diet. We finally abandoned the special diet and concentrated on social rehabilitation and genetic counselling, with the help of the psychologist and community health workers.

What is the case? Rationalize.

Karnaneedi S., Choo K.E., Ariffin W.A., Norimi M. (1989). **Phenylketonuria in a six year old Malay boy- A case report.** Med. J. Malaysia 44 (3): 248-251.

…….

Case study 2:

A one-year-old male child has conditions of global developmental delay and seizure 2nd month after birth. The child had hypopigmented scalp hair. The MRI-brain suggests of severe global developmental delay/microcephaly/seizure disorder. The diagnosis was confirmed by elevated serum phenylalanine levels 300 μmol/L (31-75 μmol/L) and low tyrosine level urine. The metabolic screening reports are positive for ferric chloride test. **What is the case? Rationalize and mention how this disorder can be treated.**

…….

Case study 3:

A one-year-child had impaired liver function (depicted by increase in serum transaminases' activities, direct hyperbilirubinemia and decrease in serum albumin level), kidney dysfunction (manifested by increase in serum levels of creatinine, urea and uric acid), and high serum levels of AFP, phenylalanine, tyrosine, methylacetoacetate and fumarylacetoacetate. Enzymes fumarylacetoacetate hydroxylase (FAH), tyrosine aminotransferase and 4-hydroxyphenylpyruvate dioxygenase were not measured because of financial constraints.

What is the name of the inborn error of metabolism? Rationalize and mention how this disorder can be treated. How is it corrected?

…….

Case study 4:

The absence of fumarylacetoacetase in biopsies of liver and kidney cortex detected immunohistochemically was noticed in newborn child. This test was recommended after detection of high levels of tyrosine and phenylalanine in both serum and urine in association with hepatorenal dysfunctions.

What is name of the inborn error of metabolism? Mention the metabolic disturbances and the metabolic agent that mainly responsible for the pathophysiology of the inborn error.

…….

Case study 5:

A 4 year old girl presenting with normal mental development without any neurological symptoms has elevated urinary excretion of p-hydroxyphenyl derivatives and blood hypertyrosinemia. An elevated blood tyrosine level was detected for the 1st time during the diagnostic procedure. The results of laboratory tests were within normal values, except for an elevated blood tyrosine (439.9μmol/L, n = 29–86μmol/L) and excretion of 4-hydroxyphenylpyruvate (pHPP) and 4-hydroxyphenyllactate (pHPL) into urine. Control laboratory tests for blood amino-acids and urine organic acids confirmed hypertyrosinemia of 535μmol/L.

What is the type of tyrosinemia? What are the recommendations to avoid the progress of the disorder and development of signs and symptoms?

…….

Case 6:

The girl was hospitalized at the age of 2 years and 5 months for diagnosis and treatment. Screening of tyrosine in the urine was positive, and serum tyrosine levels were extremely high (1879.1 mmol/l). The concentrations of tyrosine metabolites in the plasma and urine were decreased below normal level. The inborn error was characterized by ocular changes, painful skin lesions on the palms and soles, mental retardation, deposition of tyrosine crystals in the cornea and corneal inflammation, excessive tearing, abnormal sensitivity to light (photophobia) and eye pain and redness.

What is the name of the inborn error? What are other tests recommended to confirm diagnosis?

…….

Case study 7:

A child was subjected to diagnosis of inborn error of metabolism. X-rays of knee joint and vertebrae showed joint space narrowing, extensive diffuse intervertebral disc calcifications at multiple levels, disc space narrowing ochronotic pigmentation of cartilage especially characteristic in the spine. Urine turned dark on standing. The sclera of the eyes was pigmented. Ear wax exposed to air turned black on exposure to air. MRI (magnetic resonance imaging) depicted calcification of the aortic and mitral valve.

What is the name of the inborn error? What are other tests recommended to confirm diagnosis?

…….

Case study 8:

A 3 years old child is brought to clinic by his parents. The child has symptoms like intellectual disability, ectopia lentis (dislocation of the ocular lens), severe myopia, skeletal abnormalities such as excessive height and length of the limbs.

What tests do you recommend for diagnosis of this inborn error?

…….

Case study 9:

A 2 years old child was brought to clinic by his parents. The child has vascular abnormalities characterized by thromboembolism. The betaine treatment and folate and vitamin B12 supplementation successfully improved this condition.

What do you expect inborn error of metabolism to be?

…….

Case study 10:

A 46-day-old baby boy was brought to hospital. Baby developed lethargy, hypotonia and decreased oral intake on fifth day of life. Initial laboratory evaluation revealed a normal complete blood count profile, prothrombin time (PT) / activated partial thromboplastin time (APTT), normal C reactive protein (CRP) level, low blood glucose level and elevated plasma leucine and isoleucine levels. Arterial blood gas revealed metabolic acidosis. The diseased condition was improved by peritoneal dialysis and carnitine supplementation.

What is the name of the inborn error? What are the further tests recommended to confirm diagnosis?

…….

Case study 11:

A 3 year old child was referred to Hospital with mental deterioration, intermittent comas and Ecephalopathy. This inborn error was reported to be X-linked disorder and it was corrected by peritoneal dialysis, treatment with Ammonoul and decreased protein intake.

What do you expect the inborn error of metabolism to be? What are clinical laboratory tests recommended to confirm diagnosis?

…….

Case study 12:

A four-day-old male neonate with seizure and abruptly progressed coma without causing any localized neurological defects was admitted to the Intensive Care Unit because. Laboratory tests showed serum creatinine of 0.7 mg/dl and normal urine output. The tests also revealed plasma ammonia level > 397 μg/dL, normal: 27-102 μg/dl and elevated urine ammonia level.

What do you expect the inborn error of metabolism to be? What are clinical laboratory tests recommended to confirm diagnosis?

…….

Case 13:

A baby of 3 old years showed the following clinical signs: hyoketotic hypoglycemia in neonatal period, hypotonia (Low muscle tone), hypertrophic cardiomyopathy, arrhythmias, hepatopathy and finally Sudden Infant Death Syndrome.

What do you expect the inborn error of metabolism to be? What are clinical laboratory tests recommended to confirm diagnosis?

…….

Case 14:

The 2 years old baby was admitted to the hospital with Rocker-bottom feet. Clinical laboratory examination revealed elevated serum and urine glutaric, ethylmalonic, butyric, isobutyric, 2-methyl-butyric and isovaleric acids and lysine levels.

What is the name of the inborn error? What are other tests recommended to confirm diagnosis?

…….

Case 15:

The 2 years old baby was admitted to the hospital. Clinical laboratory examination revealed elevated serum and urine glutaric acids without elevations in the levels of ethylmalonic, butyric, isobutyric, 2-methyl-butyric and isovaleric acids.

What is the name of the inborn error? What are other tests recommended to confirm diagnosis?

…….

Case 16:

A male infant was the third child of healthy parents. There was no family history of metabolic disease. Pregnancy was complicated by polyhidramnios and fetal bradycardia. Cardiomegaly was detected by fetal echocardiography. Fetal morphological ultrasound showed scalp, face and neck edema. At 37 weeks, a

cesarian section was performed due to womb rupture, under general anesthesia. Birth weight was 2.7 kg (10th percentile), length 47 em (1O-15th percentile) and head circumference 34.6 cm (50-90th percentile). He had many dismorphic features, as head and neck edema, micrognathia, paucity of movement, pronounced hypotonia, bilateral cryptorchidism, micropenis, small hands, skin hyperelasticity and joint hypermobility. Initial investigations included the measurement of muscle enzymes (CPK), aspartate aminotransferase (AST) and gamma-glutamyltranspeptidase (gammaGT) (abnormal), lactate (abnormal), ammonium (abnormal), echocardiography (persistence of fetal pathways- ductus arteriosus and foramen ovale) and brain ultrasound (parenchimal echodensity). A metabolic acidosis was detected. The results of the other routine investigations, including kidney ultrasound, were all normal. Serum metabolic analyses revealed an increased value (97.5th percentile) of isovaleryl acylcarnitine, glutaril-acylcarnitine, linoleoyl acylcarnitine and 3- hydroxy-palmitoyl-acilcamitine. These findings suggested a deficit of electron-transfer flavoprotein (ETF). The urinary organic acid profile showed abnormalities corresponding to blocks in oxidation of fatty acids (ethylmalonate and dicarboxylic acids), lysine (glutarate) and branched chain amino acids (isovaleryl-, isobutyryl- and alpha methyl butyryl-glycine). The patient's condition worsened rapidly. The newborn patient had cardiac arrest and died at 7 days of age. Autopsy showed marked hepatic and cardiac vacuolisation, lipid storage myopathy and glial cell vacuolisation. Cultured skin fibroblasts measured the in vitro activity in the fatty acid oxidation pathway (deficit of electron-transfer flavoprotein). A genetic counselling was expressed to parents as the other children can have a partial deficiency of electron-transfer flavoprotein and late-onset clinical manifestation.

Domizio S., Romanelli A., Brindisino P., Puglielli C., Conte E., Domizio R., Sgarrella M. C. and Sabatino G (2005): Glutaric aciduria type II: A case report. International Journal of Immunopathology and Pharmacology 18 (4): 805-808.

Discuss and interpret metabolic changes in the above-mentioned condition

…….

Case 17:

A full term, female infant, delivered by normal vaginal delivery to 3rd degree consanguinity parents without any significant antenatal history. Baby birth weight was 3.2 kg, cried immediately after birth hence baby was shifted to mother side. Baby was brought to hospital on 4th day of life (DOL) with lethargy, poor feeding, 2 episodes of seizure and respiratory distress. Baby previous sibling died with similar presentation at 4th DOL. Baby was intubated and ventilated for 24 hours. Routine investigations were sent which was normal. Septic Screen was negative and Blood gas was s/o metabolic acidosis. HCO3 correction was given. Initial IEM work up was done which was s/o high plasma ammonia (1004 µmol/L) and ketoacidosis. Peritoneal Dialysis was done for 48 hours & Ammonia level was reduced (58 µmol/L). Urine and Plasma assessment for amino acids were sent with suspecting IEM and GC-MS of urine showed grossly elevated Isovalerylglycine suggestive of Isovaleric Acidemia. Special diet by powder formula specific for Isovaleric Acidemia (Pristine Balance Metanutrition – provides 15 gms protein/100 gms powder) and Oral Glycine (250 mg/kg/day) powder with Carnitine (100-300 mg/kg/day) was started. Baby tolerated feed well and was discharged on special diet. After 1 month of special diet for IVA there was significant reduction of Isovaleric Acid level in Urine. Significant weight gain documented on follow up. At present 18 months of age her growth and development is appropriate for age. She is following up with Bayley Scales of Infant Development III for growth and development assessment**.**

Vardhan Patel, Santosh Yadav, Mohit Sahni. A rare case of inborn error of metabolism - Isovaleric acidemia. International Archives of Integrated Medicine (IAIM), 2017; 4(12): 214-217. Available online at http://iaimjournal.com/

What is the type of hyperammonemia in such condition? Explain and Interpret metabolic changes and suggest the possible treatment of such condition.

……

Case 18

A newborn girl was manifesting on the 3rd day of life with encephalopathy, seizures and coma. She was treated with nitrogen scavenging medication (sodium phenyl acetate and sodium benzoate) and peritoneal dialysis; she responded positively to treatments.

What is the name of the metabolic disorder? What are the recommended biochemical tests to confirm diagnosis?

…….

Case 19:

The patient is a 4-year-old child received a diagnosis for Inborn Error of Metabolism. After diagnosis, he was responsive positively to treatment with betaine and to vitamins B6, B9 and B_{12} supplementation.

What is the name of Inborn Error of Metabolism? Mention other treatments that can be applied to improve the disorder.

…….

Case 20:

A female infant of two-month age noted by the parents to have darkening of the clothes, diapers and napkins moistened with urine when left unwashed for many hours. She had bluish pigmentation along the margins of the palms and tips of the fingers, pigment deposition in the sclera and black pigmentation over the ears. She responded positively to high doses of ascorbic acid, low protein diet and drug nitisinone.

What is the name of the inborn error? What are other tests recommended to confirm diagnosis?

…….

Case study 21:

A newborn child was brought by his parent to the hospital. He has very high level of plasma indirect bilirubin, severe jaundice and icterus. UGT1A1 was completely absent in his liver biopsies. The doctor recommends liver transplantation to treat this Inborn Error of Metabolism.

What is the name of congenital syndrome? Why is liver transplantation necessary for such condition?

…….

Case study 22:

Newborn child admitted to the hospital was icteric. There was no pallor, hepatosplenomegaly, or features of liver cirrhosis. Investigations revealed total serum bilirubin—12.4 mg/dL (conjugated fraction 0.7 mg/dL and unconjugated fraction 11.7 mg/dL), aspartate aminotransferase (32 U/L, normal < 40 U/L), alanine aminotransferase (normal 40 U/L), alkaline phosphatase (125 U/L, normal < 390 U/L), γ-glutamyl transpeptidase (24 U/L, normal < 49 U/L), and prothrombin time (13.9 s, control 13.2 s). There was no evidence of intravascular hemolysis. The liver biopsies indicated decreased UGT1A1 activity.

What is the name of the inborn error? How can you confirm diagnosis?

…….

Case study 23:

On clinical investigation, a child presented conjunctival jaundice and conjugated-hyperbilirubinemia without any other alterations in hepatic biochemistry and markers of liver function. The UGT1A1 activity in liver biopsies was within the normal range. His stool is pale due to decrease in urobilingen content.

What is the name of the inborn error? How can you confirm diagnosis?