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Advances in Biochemistry & Applications in Medicine

Chapter 3

Inborn Errors of Metabolism

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1. Introduction

Inborn errors of metabolism (IEM) are a group of inherited metabolic disorders leading to enzymatic defects in the human metabolism. As its name implies, inborn errors means birth defects in newborn infants which passed down from family and affecting metabolism. Hence, it is called Inborn errors of metabolism or inherited metabolic disorders. IEM can appear at birth or later in life such as phenylketonuria, albinism, lactose intolerance, gaucher disease, fabry disease etc. IEM refers a condition where in body's metabolism is affected due to genetic disorders. The cause of IEM is mutations in a gene that code for an enzyme leading to synthesis of defective enzyme activity or deficiency of an enzyme that affects the normal function of a metabolic pathway. The main indication of IEM is an excess storage or accumulation of specific metabolites in tissues, organs and blood which further manifest to health diseases. In last decades, several hundreds of different IEM have been identified. Most IEM are rare but some are life threatening. Although, most people do not know what inherited metabolic disorders are and may never have heard of them.

Therefore, in this chapter, you are going to study the basic concept, genetic basis and metabolic consequences of inborn errors of metabolism. You will learn about metabolic defective enzymes, clinical symptoms, diagnosis, and treatment of metabolic disorders of amino acids, carbohydrates, lipids, purines and pyrimidines.

Before learning to inborn errors of metabolism, it will be helpful for you to recall the basic knowledge of amino acids, carbohydrates, lipids, purines and pyrimidines, and also study about the metabolic pathways, enzymes, Mendelian Laws of Genetics from your Biochemistry and genetics textbooks.

2. Inborn errors of metabolism: Basic concept and genetic basis

The British physician, Archibald Garrod (1857-1936) coined the term inborn errors of metabolism in 1902 who discovered the first metabolic disorder “Alkaptonuria” in humans. Later, he described other metabolic disorders: albinism, cystinuria, porphyria, pentosuria. He was the first man who defined the biochemical basis of Alkaptonuria [1]. His pioneering work led to the foundation for the development of a new field of Human Biochemical Genetics. However, Garrod’s work was not well accepted in early nineteenth century because the nature of gene was not fully understood [2].

Later, George Beadle and Edward Tatum scientifically proved his findings in 1941 and proposed the one gene–one enzyme theory. This theory proposed that each gene has a genetic information to synthesize a protein (enzyme). However, this theory is generally (but not exactly) correct.

2.1 Genetic basis

Mutation in single genes is the genetic basis of inborn errors of metabolism. A mutation is the change of human genome (genes) which can arise by exposure of viruses, pathogenic bacteria, UV-radiations, unhealthy foods and environmental factors. Thus, mutations cause abnormalities in genes (genetic disorders) which consequently result in inherited human diseases. As per Mendelian Laws of Inheritance, all genotypic information is inherited from one generation to another which determine phenotypic and genotypic characteristics in human beings [3]. Most IEM are genetically-transmitted diseases result from alteration in either autosomal recessive (non-sex chromosomes) or X-linked recessive (sex-linked chromosomes). Genes disorders inherit as either dominant or recessive mode in human beings [4].

Let us understand inheritance pattern. Fig. 1.1 shows the autosomal recessive inheritance pattern of a family in which father and mother have normal two carrier genes which transfer to children. Individuals with one working copy and one non-working copy of the gene are called carriers. Recessive genetic disorders determined by two carrier genes, one inherits from the father and one from the mother. Therefore, the chance to have carrier genes in autosomal inheritance pattern is as follows:

1. Child (A) will be normal with 25% chance of inheritance
2. Child (B and C) will be 50% carrier like the parents but usually will not appear symptoms and
3. Child (D) will have 25% chance to get an inherited disorder when an individual receives the same abnormal gene for the same trait from each parent.

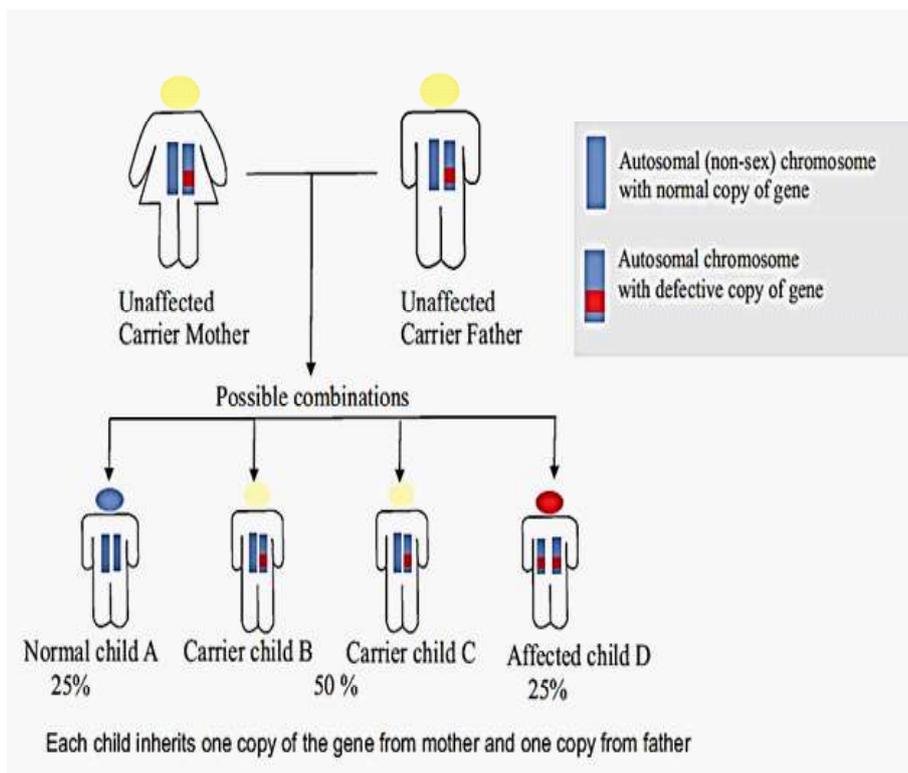


Figure 1.1: Autosomal recessive Inheritance:

Source: <http://learn.genetics.utah.edu/content/disorders/singlegene/>

3. IEM: Metabolic consequences

Let us understand how gene mutation affecting a metabolic pathway at biochemical level. As you know metabolism is basically energy production and consumption process that undergoes in a series of chemical reactions occurring within a cell. Metabolic pathways are required for maintenance of the human body in healthy state. All metabolic events are driven by enzymes that are catalytic proteins and their main function is to accelerate the rate of biochemical reactions, without being altered during that process. Enzymes play a crucial role in the metabolism of food stuffs, such as proteins, fats, and carbohydrates. If an error in the normal metabolic process due to deficiency of an enzyme caused metabolic abnormalities.

Fig.1.2 revealed the biochemical basis of inherited metabolic defect in which a gene code for an enzyme that catalyzes a specific substrate into products in a biochemical pathway. On the other hand, the gene is mutated that codes an enzyme leads to the formation of a defective enzyme. As a result, a metabolic blockage occurs in a specific metabolic pathway resulting in elevation of substrate concentration and product shortage in cells [5].

Therefore, the possible metabolic consequences of IEM are:

- Accumulation of a substrate,
- Accumulation of intermediate Metabolites,
- Lack of an essential product,
- Interfere with normal metabolic function.

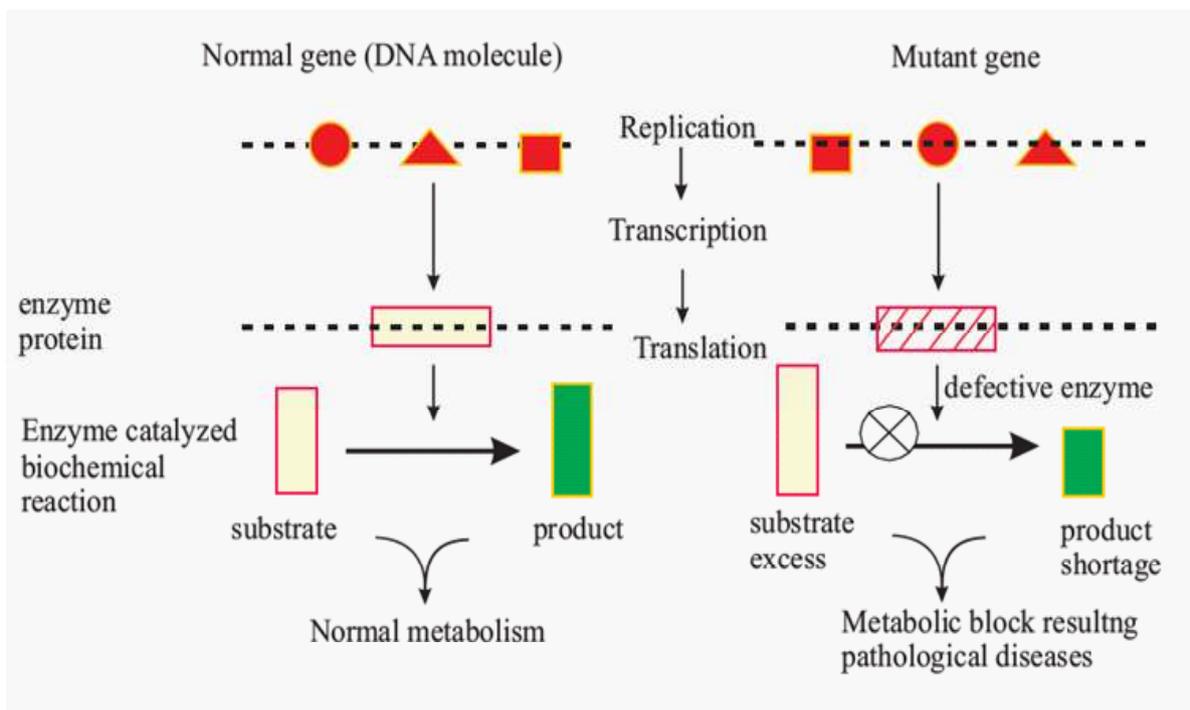


Figure 1.2: Inborn errors of metabolism

Source: <https://www.britannica.com/science/metabolic-disease>

You have studied till now genetic basis and metabolic consequences of the Inborn errors of metabolism. The disorders of IEM are classified on the basis of defect in specific enzymes involved in the metabolism of amino acids, carbohydrates, lipids, purines and pyrimidines. Let us discuss one by one.

Note: Defective enzymes are shown by \otimes red summing junction in all metabolic reactions

4. Disorders of amino acid metabolism

As you know, amino acids are the building block of proteins. Amino acid metabolic disorders are defined by accumulation of metabolic intermediates that cause specific tissue and organ damage [6]. The amino acid-metabolic disorders along with other characteristics are listed in Table 1. The chemical reactions along with enzymes involved in the catabolism of phenylalanine and tyrosine are shown in Fig.1.3. Let us discuss the disorders of amino acid metabolism.

4.1 Phenylketonuria (PKU)

Phenylketonuria is a common autosomal recessive inborn error of phenylalanine leads to intellectual disability if untreated. The estimated incidence of PKU 1 in 10,000 newborns. Phenylalanine is an essential amino acid which means it cannot synthesize in the body and must be taken from the diet. In PKU, the first step of phenylalanine catabolism is affected due to the defective catalytic activity of phenylalanine hydroxylase enzyme.

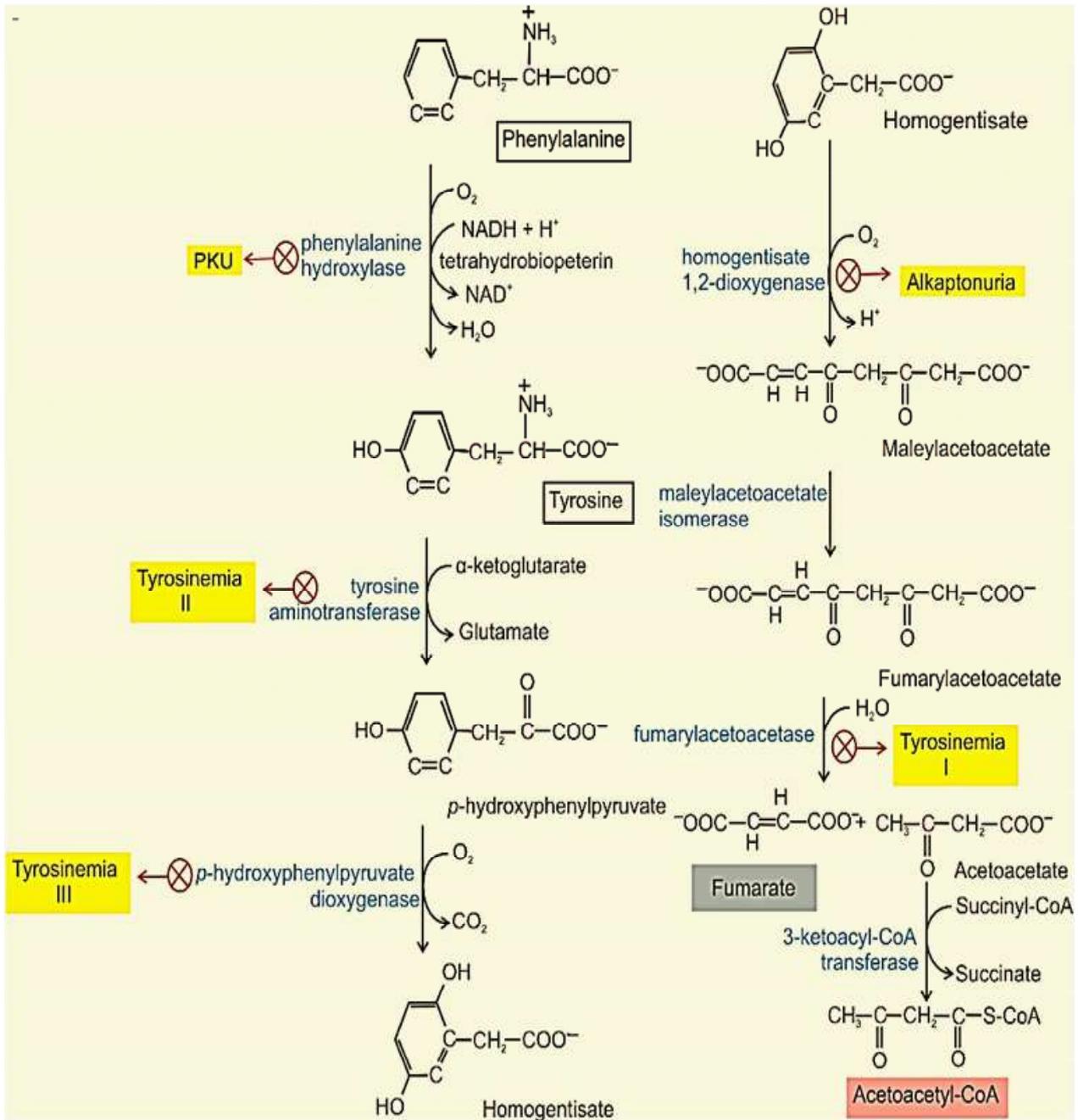


Figure 1.3 Inherited enzyme defects in catabolic pathway of phenylalanine and Tyrosine and the defective enzyme in indicated by ⊗ red summing junctions and the metabolic diseases shaded in the Yellow color (Taken from Principle of Biochemistry, Nelson & Cox, 2004).

Cause

The primary cause of PKU is deficient of phenylalanine hydroxylase, the first enzyme of phenylalanine catabolism which converts phenylalanine into tyrosine in cells (Fig. 1.4). With the deficiency, phenylalanine cannot convert to tyrosine resulting in accumulation of phenylalanine in tissues [7].

A secondary pathway (normally little used) involved in decreasing the concentration of phenylalanine in which it converts to phenylpyruvate which further is reduced or oxidized to form phenyllactate and phenylacetate respectively. Both phenylalanine and phenylacetate accumulate in tissues and blood which can excrete in urine. Hence, the name phenylketonuria.

The characteristic musty odor of urine is due to phenylacetate, which raises suspicion during infancy [8].

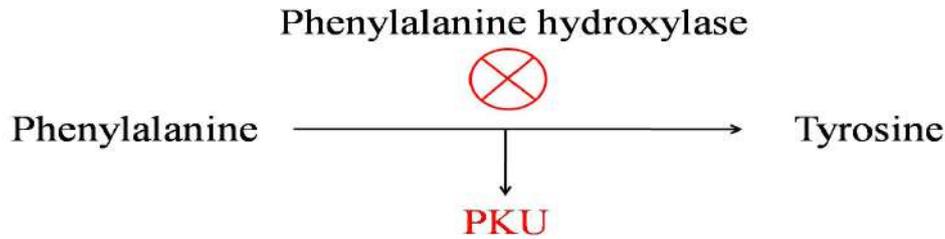


Figure 1.4

Clinical symptoms

Without effective therapy, affected people with PAH deficiency, known as classic PKU, develop profound and irreversible biochemical abnormalities such as mental retardation and neurological dysfunctions, eczema in the early life of infants. Few babies may exhibit epilepsy, Parkinson like features and decreased skin and hair pigmentation.

Diagnosis

The estimation of phenylalanine level in the blood (usually above 600 $\mu\text{mol/L}$) is primarily used to detect PKU. Increased level of Phenylalanine and phenylpyruvate in blood and urine are analyzed to confirm the PKU using Gas chromatography-mass spectrometry

Treatment

Early diagnosis of PKU in affected person is beneficial for the treatment. People with PKU may recommend restricting the intake of phenylalanine in diet for reducing the toxic effects of phenylalanine accumulation and maintain the level of phenylalanine (2-6 mg/dL) in plasma. The adjuvant therapy with sapropterin is also helpful for PKU treatment.

4.2 Alkaptonuria

Alkaptonuria is the first inborn errors of metabolism discovered by Garrod. Estimated incident of alkaptonuria is about 2-5 per million live births.

Cause

Affected people with alkaptonuria have a deficient enzyme activity of the homogentisate 1,2-dioxygenase. This enzyme metabolizes homogentisic acid to maleylacetoacetic acid (Fig. 1.5).

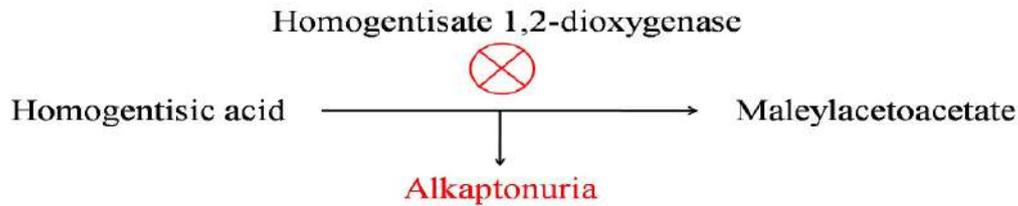


Figure 1.5

Deficient enzyme leads to abnormal accumulation of homogentisic acid in blood and tissues. High level of homogentisic acid in tissues cause a syndrome is called ochronosis. Recent findings reported that alkaptonuria is now considered a multisystemic disease starting from the third decade of life and classified as a secondary amyloidosis [9,10]. On exposure to atmospheric oxygen, urine homogentisic acid is converted into coloured compound [11] (Fig. 1.6).

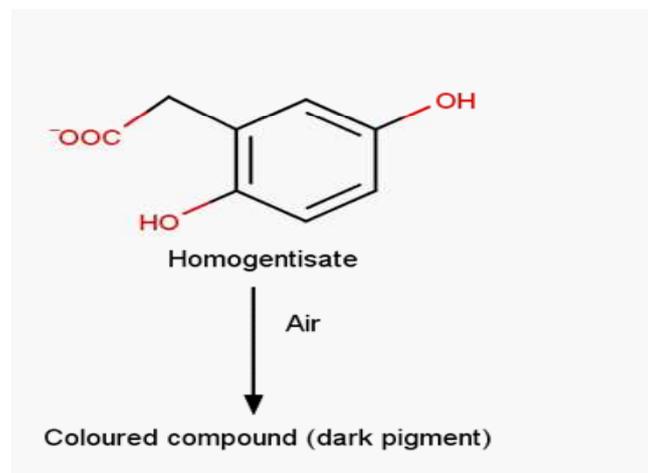


Figure 1.6

Clinical symptoms

Affected person show an abnormal level of homogentisic acid in cartilage tissue caused inflammation and arthritis in older people (Fig. 1.7) [12].

Diagnosis

The urine level of homogentisic acid is primarily measured to the diagnosis of alkaptonuria. The excretion level of HGA is usually about 1-8 grams per day in alkaptonuria's patients.

Treatment

Vitamin C and low proteins diet are recommended to control of the ochronosis by reducing the level of homogentisic acid in tissues. Newborn screening and oral nitisinone therapy may also helpful for the treatment of this disease



Figure 1.7: Nails and dorsum of hands showing bluish-colored discoloration in affected people with alkaptonuria [13].

4.3 Tyrosinemia

Tyrosinemia is also metabolic genetic disorders of phenylalanine catabolism, occur usually in newborns. This disorder results due to the absence or deficiency of enzymes involved in the multiple steps of phenylalanine and tyrosine catabolism (Refer Fig. 1.4). Untreated tyrosinemia can be fatal for life [14].

However, there are three subtypes of Tyrosinemia:

Tyrosinemia I

Lack of fumarylacetoacetate hydrolase (FAH) enzyme with inherited genetic defect results in tyrosinemia disease. This enzyme involves in tyrosine metabolism which converts fumaryl acetoacetic acid into fumaric and acetoacetic acids (Fig. 1.8). Deficiency of this enzyme, fumaryl acetoacetic acid and other intermediate precursors accumulate in the tissue and organ cause liver and renal diseases. Hence, it is also called hepatorenal tyrosinemia.

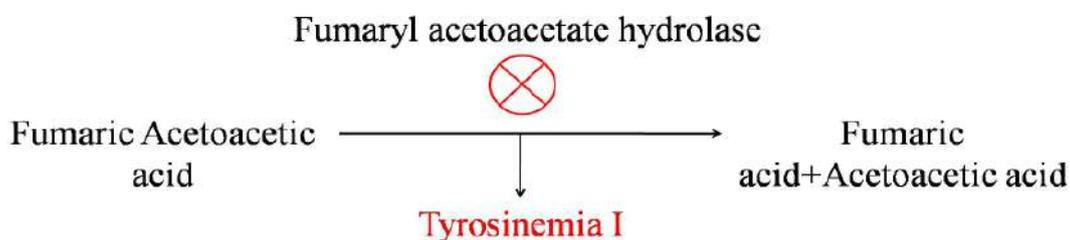


Figure 1.8

Clinical symptoms

Diarrhoea, vomiting, renal tubular dysfunction, vitamin D-resistant rickets, acute intermittent porphyria-like symptoms (abdominal pain, neuropsychiatric findings and sensitive to light), hypertension, Progressive liver and renal failure.

Tyrosinemia II

This disorder is caused by the deficiency of tyrosine aminotransferase enzyme, which catalyzes the first step in the catabolism of tyrosine forming the corresponding keto acid, p-hydroxyphenyl pyruvic acid (Fig. 1.9). Deficiency of this enzyme leads to accumulation of the tyrosine in cells and blood.

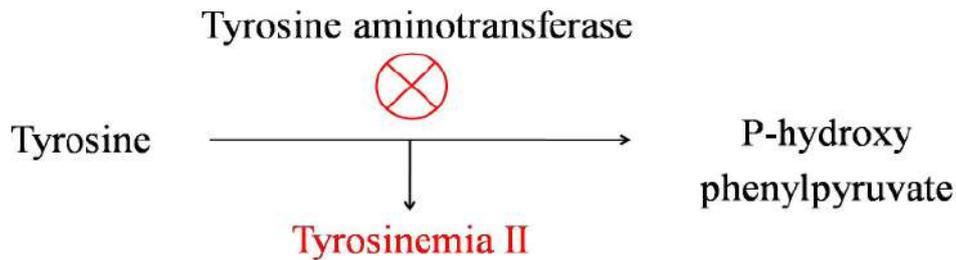


Figure 1.9

Clinical symptoms

Accumulation of tyrosine can affect on eyes, skin, and mental development. This disease begins in early childhood. Persistent keratitis and hyperkeratosis occur on the fingers, palms of hands and soles of feet, moderate mental retardation.

Neonatal tyrosinemia

Tyrosinemia Type III

This disorder occurs due to the defective enzyme, p-hydroxyphenyl pyruvic hydroxylase which normally involved in catalyzing of p-hydroxyphenyl pyruvic acid into homogentisic acid (see Fig. 2.0). The condition is more common in premature infants.

Diagnosis

Estimation of succinylacetone and tyrosine metabolites in blood and urine establishes the definitive diagnosis of Tyrosinemia I and distinguishes from other types of Tyrosinemias.

Treatment

The dietary restriction of tyrosine and phenylalanine with low protein diet may useful to control clinical symptoms of all three types of tyrosinemias. The drug, nitisinone known as NTBC has shown to be effective for the treatment of Tyrosinemia I.

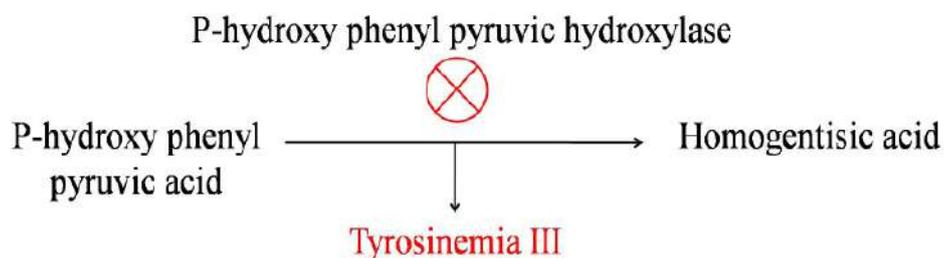


Figure 2.0

4.4 Albinism

Albinism is another congenital hereditary disorder of amino acid metabolism in which biosynthesis of melanin is defective. Melanin is a color pigment absent in certain parts of the body such as eyes, patches of skin and areas of hair. Normally, melanin is polymers of the amino acid tyrosine which gives color to skin, hair and eyes [15].

Cause

Albinism is caused by the mutation in a gene coding tyrosine hydroxylase enzyme. This enzyme converts tyrosine to 3,4-dihydroxy phenylalanine (DOPA) (Fig. 2.1). Deficient activity of this enzyme leads to albinism in which melanin formation is missing. This condition is referred to hypomelanosis [16]. The pale skin, pinkish eyes and visual abnormalities are primary symptoms of this disease.

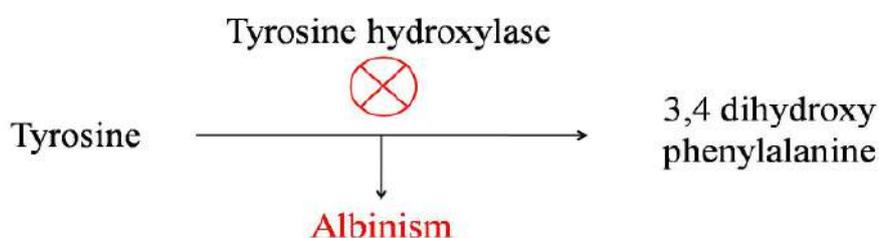


Figure 2.1

Clinical symptoms

Albinism can affect eye and skin in infants or people. This condition refers to oculocutaneous albinism (OCA) resulting in hypopigmentation of the hair, skin and eyes. Therefore, this disease leads to extremely pale skin, poor vision and white hair [17].

Diagnosis

Diagnosis is based on biochemical finding of hypopigmentation of the skin and hair. Molecular genetic testing of OCA gene is available for the albinism diagnosis.

Treatment

There is no treatment for albinism. Albino people require visual rehabilitation such as wear prescription lenses for correction of refractive errors, use hats with brims and dark glasses or transition lenses to reduce discomfort from bright light and wear protective clothing to protect skin from sun exposure

4.5 Urea cycle defects

This is an autosomal recessive inherited genetic disorder that affecting the urea cycle. The liver is a vital organ which plays a promising role in detoxification of nitrogenous wastes

by forming the compound urea through the urea cycle. Urea is a major disposal byproduct of amino acids. The disturbance in the normal urea cycle leads to accumulation of urea causing cellular toxicity (Fig. 2.2). The estimated incidence of urea cycle defects is about 1 in 8,000 live births and generally occurs in the first few days of life.

Cause

The urea cycle disorders (UCDs) are caused by defective or total absence of catalytic activity of the first five enzymes involved in the urea cycle [18]. Errors in this cycle, body unable to detoxify nitrogen content leads to abnormal accumulation of ammonia and other precursor metabolites. These enzymes are:

- Carbamoylphosphate synthetase I deficiency (CPS1)
- Ornithine transcarbamylase deficiency (OTC)
- Argininosuccinic acid synthetase deficiency (ASS1)
- Argininosuccinic acid lyase deficiency (ASL)
- Arginase deficiency (ARG)

A defect in the arginase enzyme resulting argenimia while absence of argininosuccinase and carbamoyl phosphate synthase-I may also cause argininosuccinic acidemia and carbamoyl phosphate I deficiency respectively [19].

Clinical symptoms

Infants with a severe urea cycle disorder are normal at birth but rapidly develop hyperammonemia condition resulting in neurologic damage, coma with presenting symptoms such as cerebral edema, lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, long term hyperammonemia is toxic to human beings resulting in mental retardation.

Diagnosis

Measurement the elevated level of ammonia, arginine, arginosuccinate in plasma and orotic acids in urine are used to diagnosis of urea cycle disorders

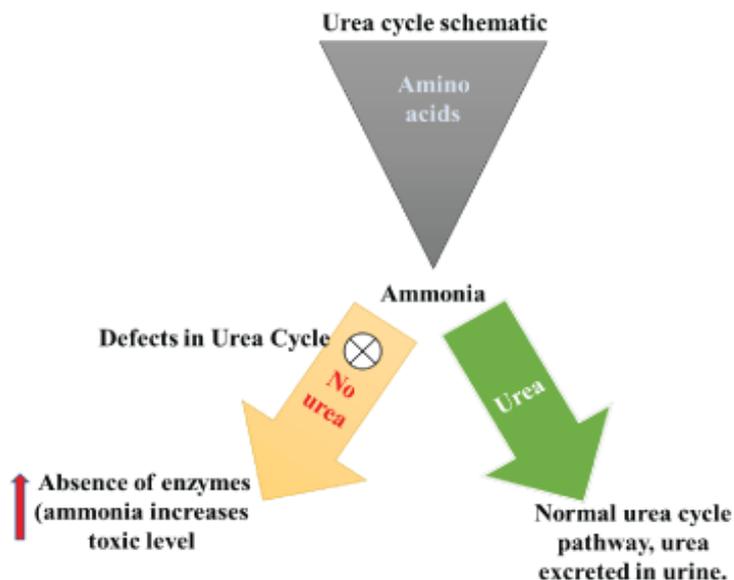


Figure 2.2 Urea Cycle defects

Treatment

Nutritional modification with low protein diet may help in controlling the level of ammonia in the body [20]. Sodium phenylbutyrate is the primary medication used to treat urea cycle disorders. This drug allows an alternative pathway to disposal of nitrogen from the body. If medicine and nutritional treatment failed, liver transplantation becomes an option for UCD’s patient.

4.6 Homocystinuria

Homocystinuria is a rare inherited disorder of metabolism of the methionine.

Cause

This disorder results due to the deficit activity or absence of cystathionine β-synthase enzyme involved in methionine degradation. In normal metabolism, methionine converts into homocysteine which further form cystathionine in presence of cystathionine β-synthase as shown in Fig. 2.3. This defect leads to accumulation of homocysteine in tissues [21].

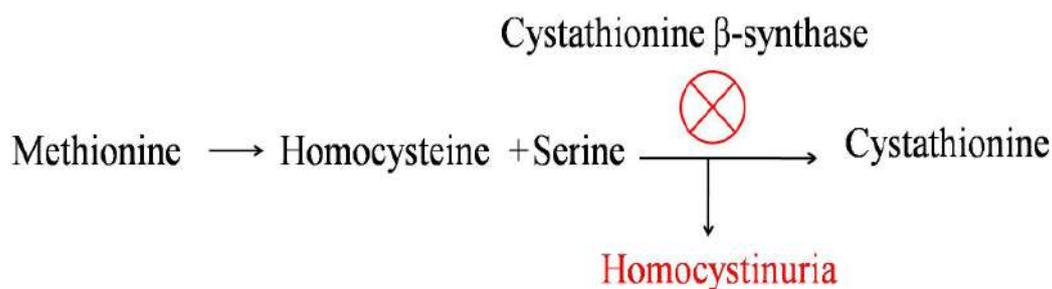


Figure 2.3

Clinical symptoms

High level of homocysteine in cells causing lipid peroxidation, fibrosis, and atherogenesis and affecting muscles, cardiovascular system and nervous system.

Diagnosis

Estimation of the level of homocysteine, total homocysteine, homocysteine-cysteine mixed disulfide, and methionine in plasma.

Treatment

Vitamin B₆ (Pyridoxine) therapy, betaine, folate and vitamin B₁₂ supplementation are used to control the biochemical abnormalities, especially to management the plasma homocysteine and homocysteine concentrations and prevent thrombosis.

4.7 Maple syrup urine disease (MSUD)

MSUD is an inherited disorder of branched chain amino acids. Affected people with MSUD have a defective gene inherited from their family.

Cause

The metabolic deficiency of branched-chain enzyme, α -keto acid dehydrogenase causes MSUD in which the body is unable to breakdown the branched-chain amino acids (BCAAs)- Leucine, isoleucine and valine. This leads to buildup keto-acids in tissues and blood resulting metabolic problem. MSUD is also called branched-chain ketoaciduria [22] (Fig 2.4).

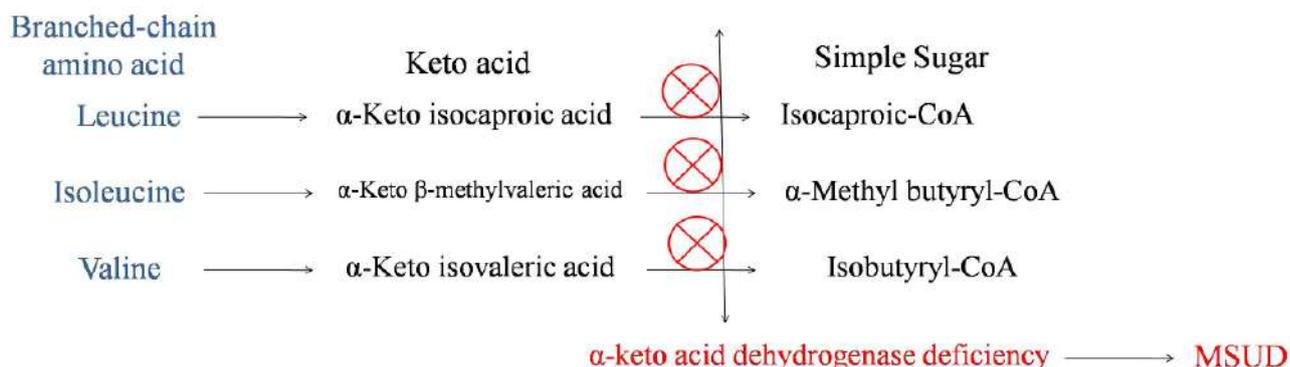


Figure 2.4

Clinical symptoms

MSUD is characterized by the sweet-smelling urine, with an odor similar to that of maple syrup. The biochemical features include neurological disorder, poor feeding, vomiting, dehydration, lethargy, hypotonia, ketoacidosis, hyperammonemia, pancreatitis, and coma.

Diagnosis

Biochemical estimation of plasma levels of BCAAs, allo-isoleucine and the urine levels of branched-chain hydroxyacids and keto-acids (BCKAs) are primary used diagnostic markers for detection of the MSUD.

Table 1.1: Genetic disorders affecting amino acid catabolism

Name of Disease	Defective process	Defective enzyme	Symptoms and clinical effects
Phenylketonuria	Phenylalanine to tyrosine	Phenylalanine hydroxylase	Vomiting and mental retardation
Alkaptonuria	Tyrosine degradation	Homogentisate 1,2- dioxygenase	Dark pigment in urine; acute arthritis
Tyrosinemia	Tyrosine degradation	fumarylacetoacetate hydrolase, tyrosine aminotransferase, p-hydroxyphenyl pyruvic hydroxylase	Diarrhoea, vomiting, renal tubular dysfunction, mental retardation
Albinism	Melanin synthesis	Tyrosine 3- monooxygenase (tyrosinase)	Lack of pigmentation: pale skin, poor vision and white hair
Argininemia	Urea synthesis	Arginase	Mental retardation Vomiting; convulsions Lethargy; convulsions; early death
Argininosuccinic Aciduria	Urea synthesis	Argininosuccinase	
Carbamoyl phosphate Synthetase I deficiency	Urea synthesis	Carbamoyl phosphate synthetase I	
Homocystinuria	Methionine degradation	Cystathionine β -synthase	Faulty bone development; mental retardation, fibrosis, and atherogenesis
Maple syrup urine disease (branched-chain ketoaciduria)	Isoleucine, leucine, and valine degradation	Branched-chain α -keto acid dehydrogenase	Neurological problems, poor feeding, vomiting, dehydration, lethargy, Vomiting

Treatment

Dietary leucine restriction, judicious supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring may help to manage people with MSUD.

5. Disorders of carbohydrate metabolism

The disorders in this group show the wide range of clinical symptoms because of abnormalities in carbohydrate metabolism. Carbohydrates are the main component of our diet

which are made up of long chains of simple sugar molecules. Normally cellular enzymes metabolize carbohydrates into glucose (a type of sugar) or simpler molecules. If an enzyme needed to metabolize a certain sugar is missing, the sugar can accumulate in the body, causing health problems. Carbohydrate metabolic disorders result due to the defect in one or more enzymes involved in carbohydrate metabolism. Let us study about carbohydrate metabolic disorders in this section.

5.1 Galactosemia

The term “Galactosemia” means high galactose level in the blood. It is a rare inherited genetic disorder of carbohydrate metabolism in which the body is unable to metabolize galactose leading to metabolic abnormalities. Although, galactose is a natural component found in milk and milk products. The incidence of this disease is about 1 in 18,000 live births.

Cause

People with galactosemia have an inherited defective gene that codes for galactose-1-phosphate uridylyl transferase enzyme. This enzyme converts galactose-1-phosphate to glucose-1-phosphate (Fig 2.5). Some other inherited defective enzymes such as galactokinase and epimerase involved in the galactose metabolism can cause galactosemia disease. Hence, galactose accumulates in the cells which further transport into blood leading to galactosemia [23].

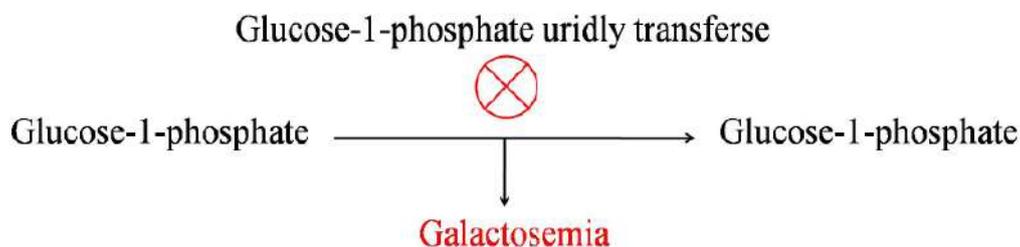


Figure 2.5

Clinical symptoms

Convulsions, irritability, lethargy, poor feeding, poor weight gain, yellow skin and whites of the eyes (jaundice) and vomiting are common symptoms.

Diagnosis

Enzymatic assay of galactose-1-phosphate uridylyl-transferase in the blood is used to detect affected people with galactosemia. Newborn screening can be done on total galactose levels in blood sample.

Treatment

The clinical symptoms of galactosemia can control with nutritional therapy mainly both galactose and lactose free diet. Infants should be fed a formula (e.g., soy formula) that contains trace levels of galactose or lactose. Continued dietary restriction of dairy products in older children is recommended for galactosemia.

5.2 Hereditary fructose intolerance (HFI)

Hereditary Fructose Intolerance (HFI) is another autosomal recessive genetic disorder of carbohydrate metabolism. Fructose is a natural monosaccharide found in many fruits, vegetables and honey.

Cause

The Acatalytic deficiency of an aldolase-B enzyme (fructose-1,6-bisphosphate aldolase) causes the HFI disease. This enzyme normally converts fructose-1-phosphate to dihydroxyacetone phosphate and glyceraldehyde in glycolysis pathway (Fig. 2.6). Deficiency of this enzyme allows accumulation of fructose-1-phosphate in the liver, kidney and small intestine resulting in metabolic inhibition of glycogen and glucose, thereby causing severe hypoglycemic condition (low sugar in the blood) in the human body.

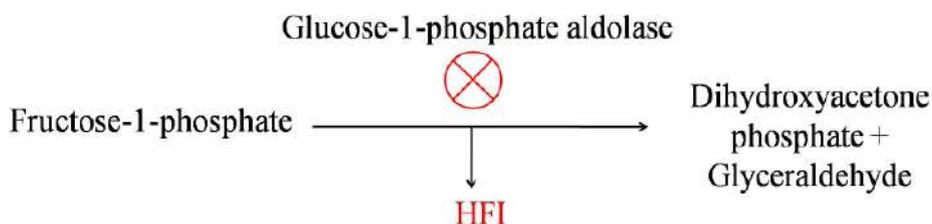


Figure 2.6

Clinical symptoms

Affected people with this disease have symptoms like abdominal pain, vomiting and weakness.

Diagnosis

The direct detection of catalytic activity of Aldolase B enzyme in liver and kidney tissue is useful for diagnosis of HFI. Recently, the diagnosis of HFI has made simpler by the PCR-based method for detection of mutated aldolase-B gene in patients [24].

Treatment

Nutritional treatment along with fructose-free diet may help to manage biochemical symptoms of HFI.

5.3 Hereditary lactose intolerance (HLI)

Lactose intolerance is a common inherited disease in childhood. Lactose, a milk sugar is metabolized by the lactase enzyme in the body. It is an intestinal enzyme which splits dietary lactose into glucose and galactose during the process of digestion (Fig. 2.7). Lactose intolerance can exhibit in children at age three [25].

Cause

Individuals with lactose intolerance is unable to digest milk and milk product due to lack or insufficient amounts of the lactase enzyme in the body. Normally, lactase breaks down lactose into glucose and galactose. With this insufficiency, lactose accumulates in the intestine wherein intestinal bacteria fermented the lactose by converting it into short-chain acids and gases like hydrogen (H_2) and carbon dioxide (CO_2) which leads to flatulence or stomach pain.

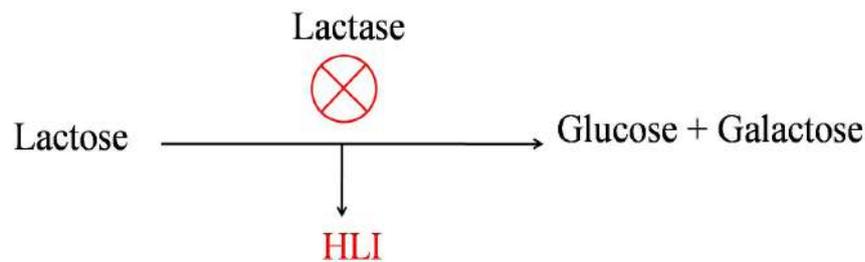


Figure 2.7

Clinical symptoms

Abdominal cramps, diarrhea, flatulence. production of gases like hydrogen (H_2) and carbon-dioxide (CO_2) are common symptoms of lactose-intolerance which leads to intestinal irritants.

Diagnosis

The direct biochemical assay of lactase activity from a jejunal sample is the most common method for the diagnosis of lactose intolerance. Molecular technique is used to identify the defective lactase gene for early diagnosis [26].

Treatment

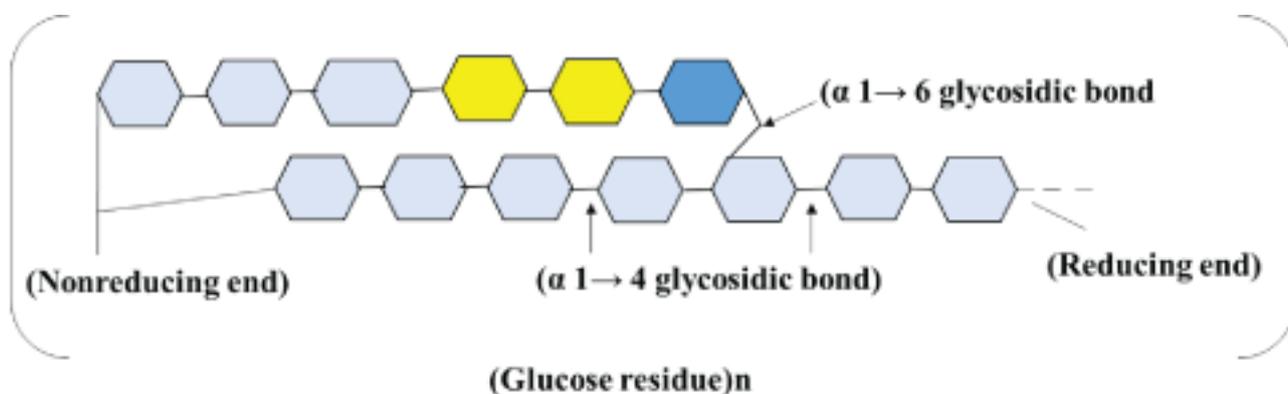
Treatment requires both fructose and lactose-free diet and limited intake of dairy products recommended for patients.

Table 1.2: Metabolic Disorders of Carbohydrate Metabolism.

Name of Disease	Substrate involved	Enzyme defect	Metabolite accumulated	Reported incidence
1. Galactosemia	Galactose	Galactose-1-phosphate uridyl transferase	Galactose-1-phosphate galactiol	1:50,000
2. Hereditary Fructose Intolerance (HFI)	Fructose	Hepatic aldolase B	Fructose-1-phosphate	1:40,000
3. Hereditary Lactose Intolerance (HLI)	Lactose	Lactase	lactose	-
4. Pentosuria	L-Xylulose	NADP-dependent xylitol dehydrogenase	L-Xylulose	1:50,000
5. Fructosuria	Fructose	Hepatic fructokinase	Fructose	1:130,000

5.4 Glycogen storage diseases (GSD)

A genetic defect in catabolic pathway of glycogen leading to develop glycogen storage diseases. Recall the structure of glucose and glycogen to understand the glycogen storage diseases. Fig. 2.8 showed the structure of glycogen consists of branched-chain polymers of glucose residues (up to 50,000) and the residues link together within chain by glycosidic bonds (α -1 \rightarrow 4 and α -1 \rightarrow 6). Glycogen is a storage form of glucose stored mainly in the liver and muscles.

**Figure 2.8** Structure of glycogen

When blood sugar level goes down, glycogen is broken down into glucose which further transports into the blood. Deficiency of enzymes involved in the glycogen metabolism result in progressive accumulation of glycogen in the liver and muscles. The most affected organ is the liver [27].

Let us discuss important glycogen storage diseases:

5.4.1 Glycogen storage disease type I (GSD-I) or von-gierke disease

In 1929, Von Gierke described the first glycogen storage disease. It is also known as Von Gierke disease.

Cause

An inherited defect in the glucose-6-phosphatase enzyme causes metabolic abnormalities in glycogen metabolism. This enzyme catalyzes glucose-6-phosphate to glucose in liver and muscles. This enzymatic defect leads to developing Von Gierke disease in which glycogen cannot convert finally into glucose molecules (Fig. 2.9). This disease is characterized by low blood sugar level and excessive accumulation of glycogen in liver and muscle. Due to absence of this enzyme,

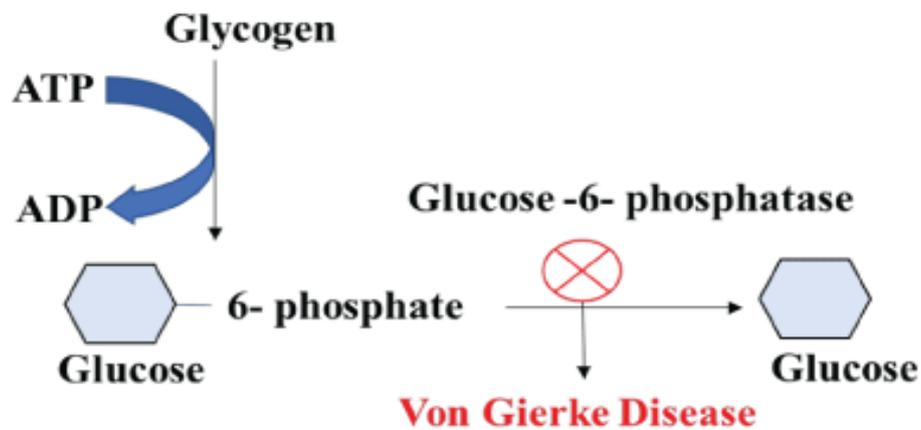


Figure 2.9

Clinical symptoms

The primary symptom in untreated infants is hypoglycemia, hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia, hypoglycemic seizures. Progressive complications are fatty liver, doll-like faces, short stature and protuberant abdomen are observed in affected people and children [28].

Diagnosis

Histological examination of liver tissues can be used to visualize abnormal glycogen content in affected people with type I disease. The detection of GSD-I gene in patients can allow for early diagnosis of this disease.

Treatment

Nutritional therapy may help to maintain blood glucose levels, to control hypoglycemia, and to provide optimal nutrition for growth and development. The nutritional interventions include frequent daytime feedings, nighttime intragastric continuous glucose infusion and oral uncooked cornstarch may necessary for the management of this disease. Liver function test must be monitored for the efficacy of dietary treatments.

5.4.2 Pompe disease or Type II glycogen storage disease

It is an autosomal recessive inheritance disorder caused by mutation in the gene coding, acid- α -glucosidase enzyme. It is also commonly shortened to GAA that stands for glucosidase acid alpha, which is the name given to the gene. This GAA gene active in lysosomes of liver, heart and muscle tissues. This disease occurs in infant, children and people who inherit a defective gene from their parents. This disease is also referred to as lysosomal storage disease.

Cause

People with the pompe disease have a deficiency of acid- α -glucosidase enzyme (Fig. 3.0). With this genetic disorder, the body cannot breakdown glycogen into the simple sugar (glucose) leading to accumulation of lysosomal glycogen in the heart, skeletal and smooth muscle, and the nervous system [29].

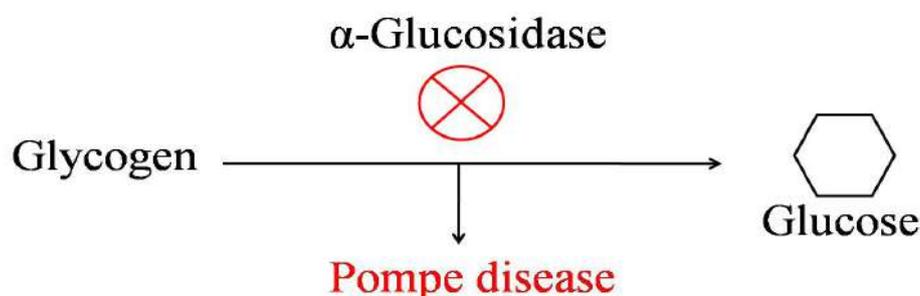


Figure 3.0

Clinical symptoms

Classical infantile-onset pompe disease symptoms can appear in infants with muscle weakness, breathing problems, feeding problems leading to failure of respiratory system and hearing loss. Without treatment or delay diagnosis, this disease can be harmful to health of the infants or children.

Diagnosis

Enzymatic assay of GAA activity in blood is the common way to confirm the Pompe disease in patient. GAA mutation analysis is confirmatory test for diagnosis of this diseases.

Treatment

Nutritional therapy may provide temporary improvement in patient with Pompe disease but early diagnosis is better option for the treatment. Enzyme replacement therapy (ERT) with Myozyme® or Lumizyme® (alglucosidase alfa) can become new treatment options for affected people with the Pompe disease [30].

5.4.3 Type III or Cori disease

Glycogen storage disease Type III is known as Cori disease. It is an inherited, an autosomal recessive genetic disorder caused by a mutation in the gene coding debranching enzyme “amylo (α -1 \rightarrow 6) glucosidase” which is a key enzyme to split branched-glucose molecules from glycogen in glycogen degradation. The conversion of glucose to lactate in the muscles and lactate to glucose in the liver is called the Cori cycle [31].

Cause

People who lack the debranching enzyme leading to develop the Cori disease. This disease causes progressive accumulation of glycogen which impaired the physiological functions of organ and tissues particularly, in liver and muscle (Fig. 3.1).

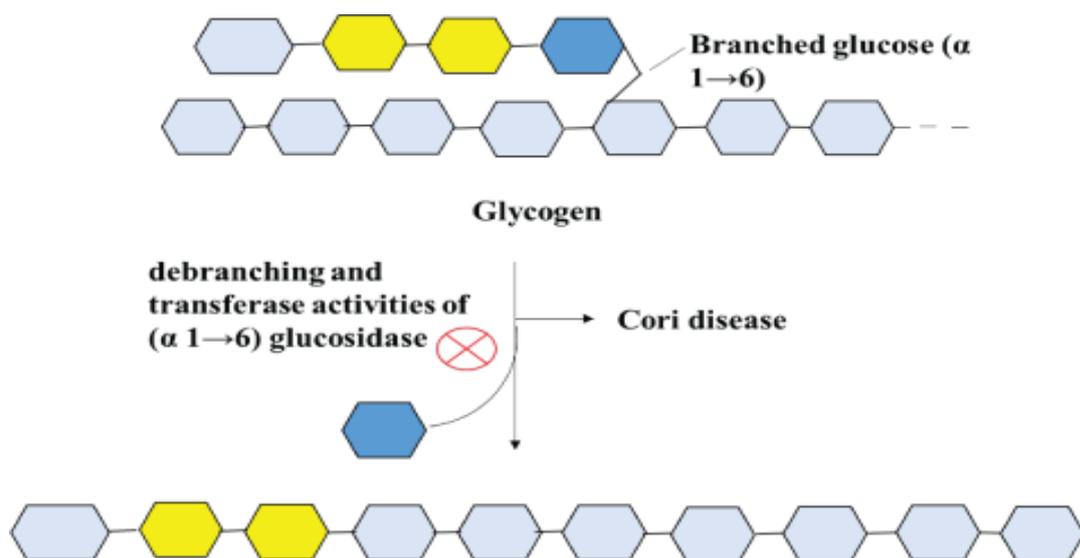


Figure 3.1

Clinical symptoms

The dominant clinical features of this disease are hepatomegaly, hypoglycemia with fasting and its clinical significance ranges from asymptomatic in the majority to severe cardiac dysfunction, congestive heart failure, and (rarely) sudden death [32].

Diagnosis

Elevated serum concentrations of transaminases and CK are the hallmarks of GSD III. The debranching enzyme activity test and histopathology examination are useful for the definitive diagnosis of Cori diseases.

Treatment

GSD III's patients treated with high protein diet to control the clinical symptoms. Currently, there is no effective treatment for progressive hepatomegaly

6. Disorders of lipid metabolism

Inherited genetic defects in the lipid metabolism leads to excess storage of lipids in ectopic tissues, such as skeletal muscle, liver, and heart, seems to associate closely with metabolic abnormalities and cardiac disease. Storage disorders involve in specific enzyme deficiency in lysosomal degradation pathways. In fact, most lipid metabolic disorders arise from inherited defect in the catabolism of sphingolipids. The lipid-like sphingolipid is a constituent of cell membrane primarily rich in brain cells. Fig. 3.2 shows some disorders in degradative pathway of membrane lipid sphingolipids and inherited defective enzymes.

Let us discuss biologically important lipid metabolic disorders.

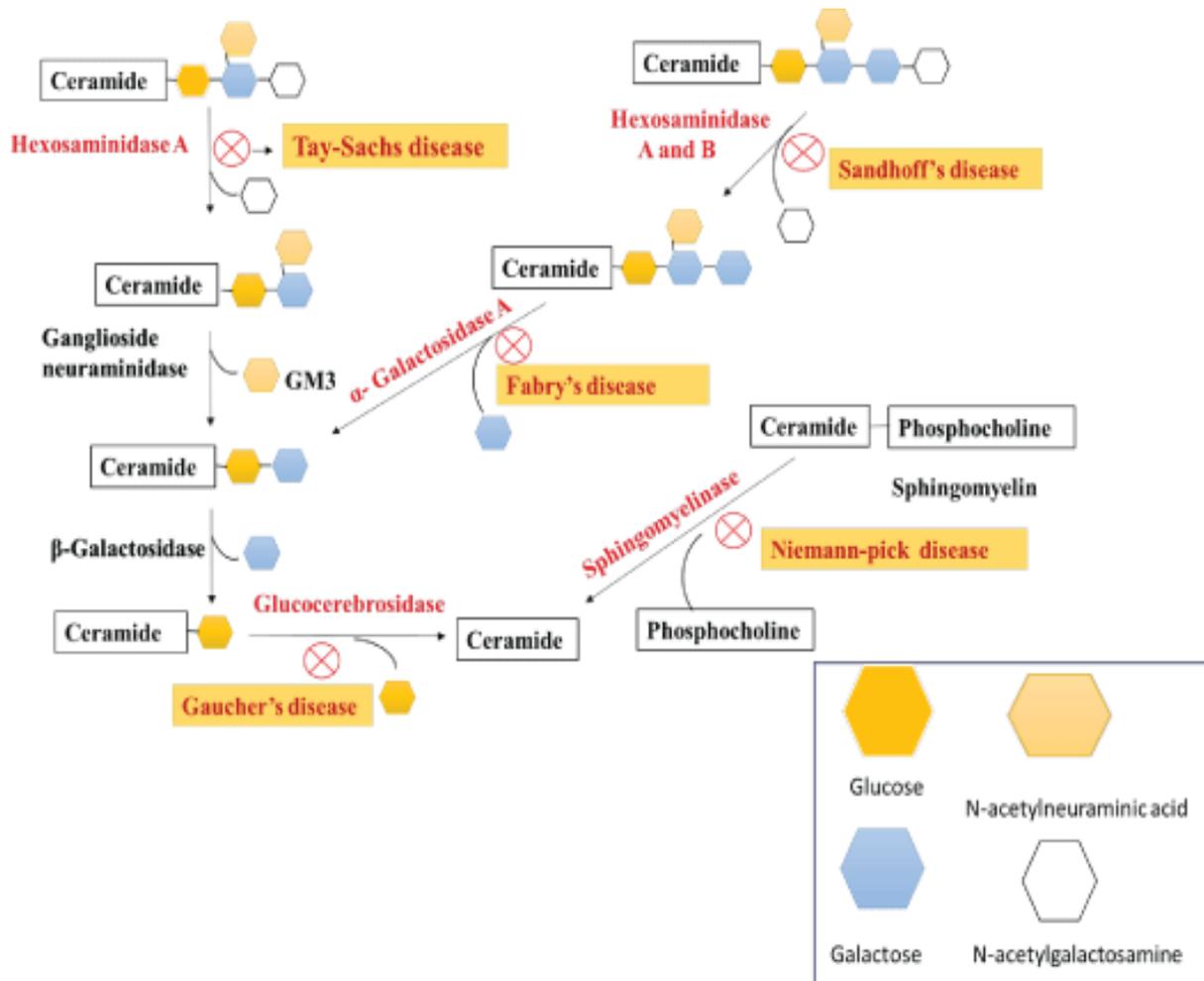


Figure 3.2: Metabolic defects in the Sphingolipid metabolism (Courtesy: Nelson & Cox, 2008).

6.1 Gaucher disease (Glucosyl ceramide lipodosis)

In 1882, the French physician Philippe Gaucher described the first lipid storage disease in lysosomes and hence the name is referred as Gaucher Disease. Overall, the estimated incidence is about 1 in 7000 live births.

Cause

Glucocerebroside metabolism is caused by the β -glucocerebrosidase enzyme deficiency, which normally breakdowns glucocerebroside into glucose and ceramide (Fig. 3.3). With the

deficiency, glucocerebroside accumulates in lysosomes and macrophages resulting in enlargement of cells. These abnormal cells are called Gaucher cells [35].

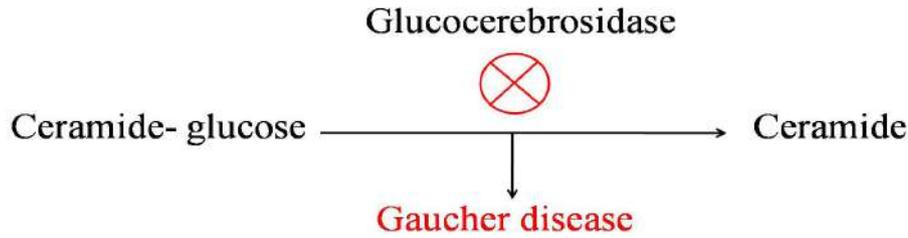


Figure 3.3

Clinical symptoms

The common features of this disease are osteopenia, sclerotic lesions, hepatosplenomegaly, anemia, thrombocytopenia and lung disease which may finally affect in proper functioning of central and peripheral nervous system.

Diagnosis

The test for determination of deficient activity glucocerebrosidase enzyme in the blood and analysis of β -glucocerebrosidase enzyme gene may reliable for the diagnosis.

Treatment

Enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) is available as the first effective treatment for Gaucher disease.

6.2 Fabry disease

Unlike most other sphingolipidoses, Fabry disease is an inherited X-linked recessive lysosomal storage disorder, occurring mostly in adults. The Johannes Fabry and Anderson discovered Fabry disease in 1998 hence, it is also referred to as Anderson-Fabry disease. The estimated incidence is about 1 in 40,000 live births.

Cause

Genetic mutation in a gene encoding α -galactosidase, a lysosomal enzyme leads to develop Fabry disease (Fig. 3.4). Deficiency or low activity of α -galactosidase-A enzyme causes abnormal accumulation of sphingolipid in lysosomes leading to a wide range of clinical adverse effects including renal, cardiac, cerebrovascular and skin disorders [34].

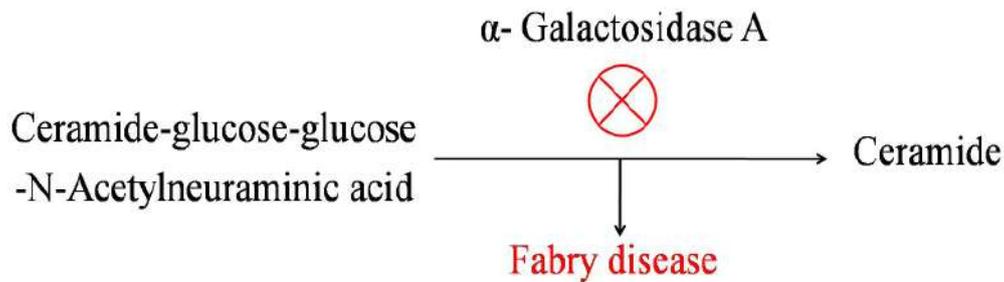


Figure 3.4

Clinical symptoms

If untreated, affected people with Fabry disease have average life expectancy about 15-20 years. The classical symptoms include renal failure, cardiovascular dysfunction, neuropathy, stroke and skin disease.

Diagnosis

Demonstration of marked α -galactosidase A deficiency in blood or tissues is the definitive method for the diagnosis. Molecular analysis of GLA enzyme gene can also be done to diagnosis.

Treatment

Enzyme replacement therapy along with medicine may useful for preventing the symptoms of Fabry disease.

6.3 Niemann-pick disease (Sphingomyelin lipidosis)

Niemann-Pick disease is another lipid storage disorder which was first described by Niemann and Pick. It is also known as sphingomyelin lipidosis. It is an autosomal recessive genetic disorder in which the body unable to metabolize of sphingomyelin in cells. Due to lack of lysosomal sphingomyelinase human cells cannot metabolize sphingomyelin. This stage leads to abnormal storage of sphingomyelin primarily in lysosomes. Hence, it is called lysosomal storage disorders. Lipids like sphingomyelin and cholesterol present in all cell membrane and metabolize in lysosomes [36].

This disease is classified into two types:

Niemann-Pick Type-A disease results in neurological dysfunctions in infants and hepatosplenomegaly.

Niemann-Pick Type-B affects visceral system with little to no neurological detriment.

Cause

Both diseases (Types A & B) are caused by inherited defect in the lysosomal sphingomyelinase enzyme, which normally breakdowns sphingomyelin into phosphorylcholine and ceramide (Fig. 3.5).

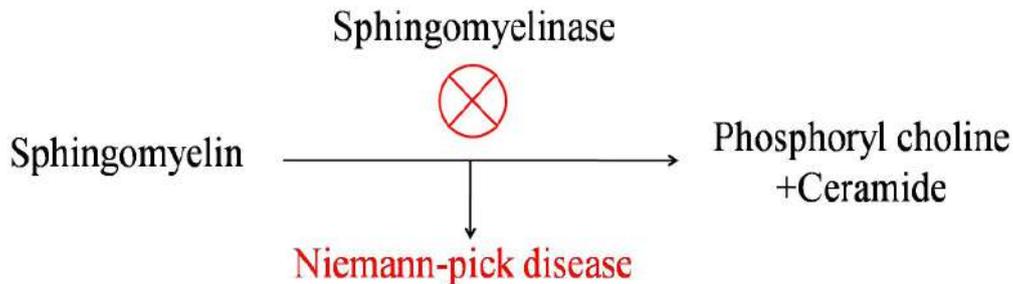


Figure 3.5

Clinical symptoms

Include enlarged liver and spleen, mental retardation, a classic cherry-red spot in the retina and early death.

Diagnosis

The diagnosis is established by detection of sphingomyelinase enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts.

Treatment

Adequate nutrition with low- cholesterol diet is recommended for supportive treatment to manage the symptoms of NPC diseases. There is no effective treatment for NPC diseases, but stem cell transplantation may help to cure the Type-A and Type -B diseases.

6.4 Tay-Sach's disease (TSD) (Ganglioside lipidosis)

This disease is an inherited disorder of lipids particularly sphingolipids in which lipids accumulate in the cells leading to health problems. Gangliosides are glycosphingolipids contain a fatty acid, sphingosine, oligosaccharide chain. It is rich in the nerve cell membrane.

Cause

Tay-Sach's disease results from a genetic defect in the hexosaminidase-A enzyme (Hex-A). This is a vital enzyme which cleaves glycosidic bond attaching N-acetyl-hexosamine in ganglioside GM2 (Fig. 3.6). Due to the absence of Hex-A enzyme, GM2 cannot convert to GM1 resulting in accumulation of sphingolipids in brain leading to degeneration of the nervous system [33].

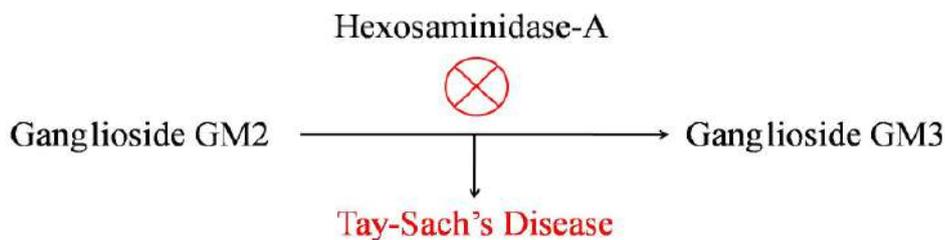


Figure 3.6

Clinical symptoms

The symptoms of Tay-Sachs disease begin between ages three and six months with progressive weakness, growth retardation, loss of motor skills, paralysis, blindness, Without treatment, death, usually by 3 to 4 years. More than 90 % of the patients with this disease have a characteristic cherry-red spot in the retina.

Diagnosis

The determination of hexosaminidase-A enzyme activity (HEXA) in the serum or white blood cells is the common biochemical marker for Tay-Sachs disease. Molecular genetic testing of HEX-A enzyme gene is the best accurate method for diagnosis of Tay-Sach's disease.

Treatment

Affected people with this disease needs to support with adequate nutrition and hydration. Genetic analysis and enzymatic screening programs can help to control this disease.

7. Disorders of purine and pyrimidine metabolism

Inherited defective genes cause enzymatic deficiencies in purine and pyrimidine metabolism. As you know, purine and pyrimidine are nitrogenous bases that form nucleic acids (DNA and RNA). Let us discuss first purine metabolic disorders.

7.1 Lesch-nyhan syndrome

A genetic lack in hypoxanthine-guanine phosphoribosyl transferase (HGPRT) enzyme activity results in Lesch-Nyhan syndrome. Although, it is a rare syndrome caused by a mutation in the *HGPRT* gene located on the X-chromosome. HGPRT involves in the salvage pathway in which purine and pyrimidine are recycled from free purine and pyrimidine nitrogenous bases. This enzyme helps to convert hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP). The final step of this pathway, xanthine oxidase enzyme converts hypoxanthine to xanthine which is further oxidized to uric acid and it excretes primarily in the urine (Fig. 3.7). This syndrome leads to excessive accumulation of uric acid in

cells causing toxicity. The most affected organ is the brain [37].

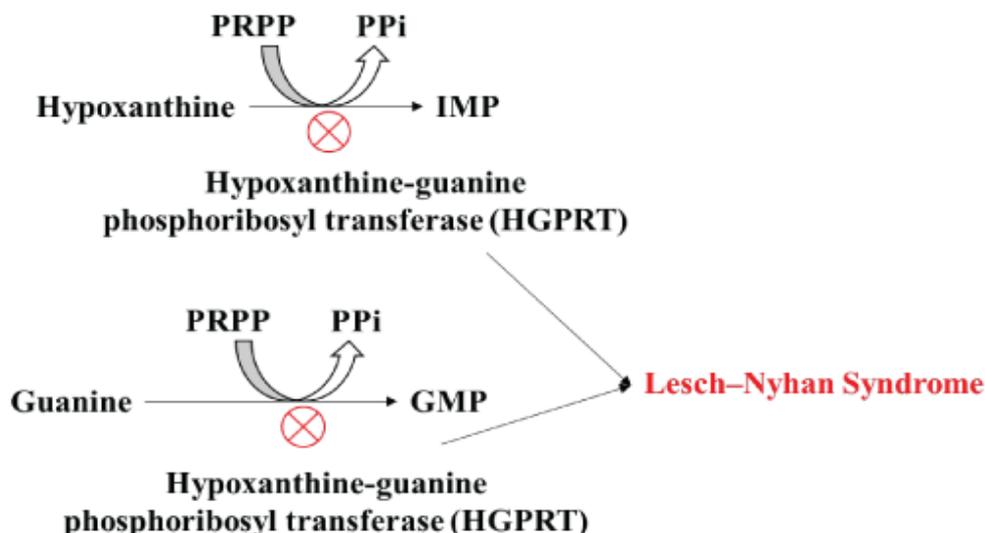


Figure 3.7

7.1.1 HGPRT deficiency leads to gout disease

Gout is a common disorder associated with HGPRT deficiency which is characterized by high level of uric acid in the blood (hyperuricemia). Uric acid is an end-product of the purine degradation. In the blood, most uric acid is present in the form of monosodium urate. High levels of urate deposit in crystal form in tissues resulting skin nodules (tophi), joint pain, kidney damage and stones. The normal level of uric acid is 3-7 mg/dl in blood when its level is more than 7 the condition is called hyperuricemia. Urate crystal saturates in the tissues and joints caused a serious clinical problem.

Clinical symptoms

The most common clinical features include hypotonia and developmental delay are evident by age three to six months in affected children. Persistent self-injurious behavior (biting the fingers, hands, lips, and cheeks; banging the head or limbs) is a hallmark of the disease. Abnormal disposition of urate crystals in joints can cause joint pain and acute arthritis.

Diagnosis

Estimation of high urate concentration and HGPRT enzyme activity in serum are the main diagnostic tool for prompt diagnosis. A urinary urate-to-creatinine ratio greater than 2.0, indicating uric acid overproduction (hyperuricemia), is a characteristic for children younger than age ten years. HPRT1 is the only gene known to be associated with Lesch-Nyhan syndrome.

Treatment

The high rich diet of meat and seafood containing uric acid should be restricted. Allopurinol drug can use to treat people with gout and this drug inhibits xanthine oxidase activity and reduces the formation of uric acid. Non-steroidal anti-inflammatory drug (NSAID) may recommend to reducing the clinical symptoms of the gout disease.

7.2 Adenosine deaminase deficiency

The adenosine deaminase deficiency is known as the Severe Combined Immunodeficiency (SCID). The SCID is an autosomal recessive disorder results from mutation in the gene encoding adenosine deaminase (ADA) enzyme which converts adenosine to inosine in the purine catabolism (Fig. 3.8) [38].

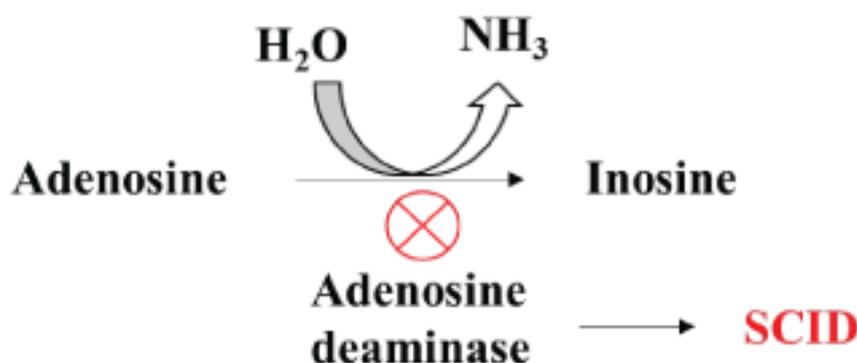


Figure 3.8

This enzyme is present in a variety of cells, mainly lymphocytes cells. ADA deficiency leads to accumulation of adenosine and rises dATP levels resulting in depletion of lymphocytes cells. It also decreases production of T cells, B cells and natural killer cells (NK cells). The incidence of ADA deficiency is approximately 14%. Untreated children with this disorder usually die by the age of two.

Clinical symptoms

Usually present with failure to thrive, opportunistic infections, persistent diarrhea, extensive dermatitis and recurrent pneumonia.

Diagnosis

Estimation of ADA catalytic activity in blood cells confirmed the diagnosis of deficiency of ADA. Molecular genetic analysis of ADA gene can be performed for the ADA deficiency.

Treatment

Bone marrow transplantation is the best option for the treatment of SCID. Bovine ADA has been shown to be beneficial for appropriate therapy for SCID's patients.

7.3 Disorders of pyrimidine metabolism

7.3.1 Orotic aciduria

This is an inherited autosomal recessive disorder caused by a deficiency of UMP synthase, a bifunctional protein includes the enzyme activities of orotate phosphoribosyl transferase and orotidine-5' phosphate decarboxylase which catalyze orotate to OMP and OMP to UMP respectively (Fig. 3.9). With the deficiency, orotic acid accumulates in tissue and is excreted in urine. Abnormal accumulation of orotic acid leading to significant clinical health problems [39].

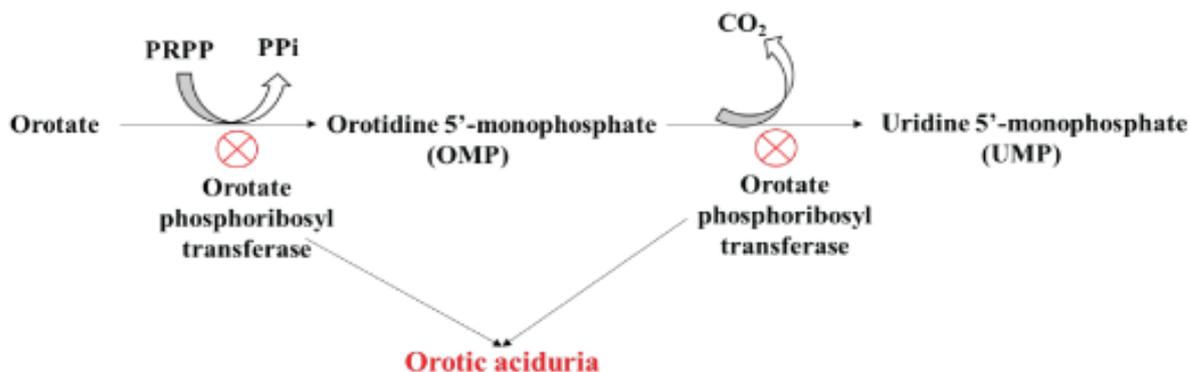


Figure 3.9

Clinical symptoms

Megaloblastic anemia, oroticrystalluria, nephropathy and cardiac malformations are common clinical features of this disease.

Diagnosis

Gas chromatography-mass spectrometry is used to analyze the level of urinary orotic acid for detection of this disease.

Treatment

Replacement therapy with uridine usually leads to a clinical and hematologic remission and reduction in the urinary excretion of orotic acid. Allopurinol is useful to reduce orotate level and uric acid excretion in affected people with this disease.

8. Summary

- The inborn errors of Metabolism (IEM) are significantly interrelated with genetic abnormalities. The inheritance pattern of genes may be either dominant or recessive which inherit from carrier parents to their children. In other words, defective genes lead to synthesis of defective enzymes. The basis of EMI is the gene mutation in single genes that code for an enzyme resulting in synthesis of deficiency of a specific enzyme involved in metabolic pathway of amino acids, carbohydrates, lipids, urines, and pyrimidines.

- Absence or deficiency of enzymes in metabolism lead to blockage in individual steps

of normal metabolic pathway resulting in biochemical abnormalities. As a result, intermediate metabolites accumulate in tissues and bold system which consequently affecting the biochemical and physiological functions of the cells and vital organs of the body and its consequences progressive Health problems arise. Clinical symptoms of IEM may appear with few days in affected people or newborns resulting in physical and mental abnormalities in human beings.

- Early diagnosis, genetic analysis of newborns, screening of future parents and nutritional treatment may help in reducing the chance to develop clinical symptoms and to management of the inherited metabolic disorders

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