Genetic Metabolism Disorders in Newborn

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ABSTRACT

Babies with any type of metabolic disorders lack the ability to break down the food well, which may induce too little amino acids, phenylalanine and blood sugar to the body, there are numerous kinds of this disorders, most of babies with a genetic metabolic disease have many mutation in gene that coded an enzyme which results a deficiency in same enzyme are hundreds of these disorders and they were diagnosed by their symptoms and the treatment method. The treatment methods of the metabolic disorder depend on the specific type of disorders, inborn metabolic disease are some-time treated with dietary guidance, and other childcare choices, many hereditary metabolic disease are initially caused by gene mutations and that transferred from parents to offspring.

Keywords: Genetic Disease, Newborn, Metabolism Disorders.

I. INTRODUCTION

Metabolism refer to all chemical process in the body that breakdown the basic food ingredient enzymatically to produce energy. In more cases the newborn suffer with more disease correlated with metabolic abnormality since birth, it may look normal at the beginning but if this disease is not treated the children will suffer of many conditions it may be fatal, somehow if they found out the disease in early stage it is possible to reduce their effect without any risk on the life of babies [1,2].

A single enzyme is either not released by the body at all in the most genetic metabolism disorders, or is released in a manner that does not function correctly, the messing enzyme is like as absent production line worker, depend on the role of the enzyme, its absence means toxic chemical may develop or that that an essential product may not be produced[3].

Food which is not breakdown correctly causes accumulation of many chemical intermediate compound in various section of the body, and thus causes many health problems, and this is because deficiency of defect of enzyme required for metabolism of food[4].

In the general population the genetic metabolic condition is very uncommon, inherited metabolic disorders taken together can impact between 1 in 1,000 – 5,000 newborn. There are more 40 metabolic disorders it is classified into major groups according to type of metabolic pathway, and differ presence percentage in every society[5,6], it will be explained in detail.

1-Amino Acid Disorders

Amino acids consider a basic unit for proteins and which have many function inside the body, and the genetic disorders that correlated with amino acids metabolism may be occur as a lack of the ability to breakdown the amino acids of from un ability to use this amino acid inside the cells, and there are many types of genetic disorders associated with error in amino acids metabolism[7,8].

1-1- Phenyl Ketonia disorders

It is considered of metabolic abnormality that associated with amino acid phenylalanine, if this disorders is not diagnosis early and treated causes many clinical symptoms, like damage of brain cell and mental retardation as a result of accumulation of phenylalanine in the blood. And his injury rate about 1:2,500 for all birth in the world[8,9].

1-2-Maple Syrup Urine Disease (MSUD)

This disorder caused by defect in the activity of Branched-chain Alpha-keto Acid Dehydrogenase enzyme. And therefor increased levels of amino acids (Leucine, Isoleucine and Valine) in the blood, but if this disorders is not early treated causes various symptoms like vomiting, loss of body fluids and brain malfunction. Past genetic studies have found MSUD to be an autosomal recessive disorders caused by pathogenic variants in BCKAD genes encoding the components E1 α, E1 β , E2 , and E3. Prevalence about 1:80,000 of births [1,10].

1-3-Homocysteinuria disorders

This disease result occurs decrease in the activity of Cystathionine B-Synthase enzyme and causes accumulation of methionine because it does not convert into cysteine. And this increase of methionine causes damage in connective tissues, muscle, CNS and cardiovascular[11] (Braconi et al., 2016). CBS-deficiency homocystinuria is an autosomal recessive cond ition the human CBS gene has been mapped to 21q22.3. to date more than 150 different mutation have been identified in the CBS gene, the II278Thr is the most common mutation among the world, It spread in the world about 1:3,000 for all births[12,13].
1-4-Tyrosinemia class I disorders

Tyrosinemia class I happen as a result from lack of Fumarylacetoacetate Hydrolase enzyme, this enzyme play a vital role in the metabolic pathway of amino acid tyrosin, if not treated causes death within first year. The gene encoding FAH enzyme located at chromosome 15q23, consist of 14 exons. Approximately 100 different mutations responsible for HT-1 have been identified in FAH gene. And the research identified about 100 separate mutation responsible for this disease. World-wide, this disease estimated 1:90,000 of all birth[14,15].

1-5-Argininosuccinic Aciduria disease

This disorders caused due to defect activity of Argininosuccinate Lyase enzyme which is catalase the reaction convert of argininosuccinate into arginine and therefore increase level of argininosuccinante in the blood and causes many symptoms like vomiting, coma, damage in CNS and nausea. ASL gene coded this enzyme and located on chromosome 7q11.2, about 35 killo-base long with 17 exons. Mutation in this gene showed to cause ASuria, prevalence of approximately 1:70,000 for each births in the world[16,17].

1-6-Deficiency of Argininosuccinic Synthetase enzyme (Citrullinemia) Disorders

This disorders occur as a result deficiency of Argininosuccinic synthetase enzyme, this enzyme catalase the third step of urea cycle and that include convert the amino acids aspartate and citrulline to immediate compound called argininosuccinate, and any defect of Argininosuccinic synthetase enzyme lead to incomplete urea cycle properly. Both parents were found to have the recognized mutation in exon 15 that change gly390 arg of the ASS1 gene at chromosomal position 9q34.1 thereby confirming the cirtullinemia. Symptoms of this disease a lot and the most important increase level of ammonia in the blood, and that causes many healthy problems. This disorders diffuse in the community in the rate of 1:57,000 of the births[18,19].

1-7-Histidinemia Disease

Any defect of the activity of histidase enzyme causes disorders called histinemia, histidase enzyme play an important role in convert amino acid histidine to urocanic acid, and the symptoms of this disease include damage in brain cell and difficulty speaking, the gene, which encoded this enzyme, located at 12q22--q24.1. Prevalence is 1:12,000.[8,13].

II. FATTY ACID DISORDERS

The fatty acids consider a main source of energy production inside the cells, and there are numerous enzymes helps the body to decomposition the fatty acids, and any change in this enzyme may cause a defect in the metabolism of fatty acids, and following damage organs and lack the energy inside the body[7,20].

2-1-Deficiency of Carnitine Plamtyoyntransferase Type I

This disorder occurs due to deficiency of Carnitine plamtyoyntransferase enzyme, which is catalase the reaction to bind the hydrophobic end of fatty acid to carnitine to produce compound called Acyl-Carnitine, and the transfer to the mitochondrial membrane. Transmission is autosomal recessive. Genetic counseling should be proposed to parents of an affected individual informing them of the 25% chance the offspring has of inheriting the disease-causing mutations, this disease causes low level of ketone and sugar in the blood, liver enlargement, muscle weakness and the accumulation of fatty acid in the blood causes damage in important organs in the body like liver, brain and hart. Its considers rare disorders[21,22].

2-2-Carnitine Uptake Deficiency Disorders

The decrease in the level of the Carnitine Transport enzyme causes this disorders, it has a major role for transport the carnitine inside the cell through the cell membrane. Nevertheless, further confirmation of the diagnosis depends on the SLC22A5 gene for molecular genetic testing, sequence review is scientifically available an can detect the least one mutation in about 70% of the individuals affected, this disorders causes decrease level of ketone, sugar increase level of carnitine in the blood, and the accumulation of fatty acid causes damage in brain cell and liver enlargement, present in newborn with rate 1:150,000[5,23].

2-3-Deficiency Trifunctional Protein Disease

The name of this disorders derived from a compound made up of 3 enzymes, and there are two genes encoded these enzyme which responsible for breakdown of fatty acids inside the mitochondria, any polymorphism or mutation in these genes leads to decrease in levels and activity of trifunctional proteins, Some studies explains the clinical and biochemical result of TPD patients and four novel mutation of the genes HADHA and HADHB, the symptoms of this disorders causes loss of energy, decrease sugar in the blood, difficulty breathing and finally death of the child, it is considers a rare disease[24,25].

2-4-Deficiency of Medium Chain Acyl-CoA Dehydrogenase (MCADD) Disorders

This disease as a result of lack the activity of the medium chain Acyl-CoA dehydrogenase enzyme, and who is responsible for analyzed of fatty acid chain inside the mitochondria to production energy. In these cohorts the A985G mutation in the ACADM gene accounted for about 90% of disease causing alleles, beside this common mutation in Europe, other mutation particularly T199C are frequently found in other patients, the symptoms associated with loss of energy, decrease sugar level in blood, problems in heart and liver and sudden death, presence in children 1:15,000[22,26].

2-5-Hydroxy Acyl-CoA Dehydrogenase Deficiency (MFSCHADD) Disease

This disorders associated with defect of 3-Hydroxy Acyl-CoA Dehydrogenase enzyme, and play a vital role for breakdown of the short chain fatty acid to production the energy inside the mitochondria, symptoms
of this disorders involve energy loss, hypoglycemia, difficult in breath and if not treated causes death[5,22].

2-6-Deficiency of Short Chain Acyl-CoA Dehydrogenase disorders

This disease caused by decrease in level of Short Chain Acyl-CoA Dehydrogenase enzyme, which is accountable for destruction of Short Chain fatty acids inside the mitochondria for make energy. In an autosomal recessive form, SCADD is inherited. Each sib of an adult with SCADD has 25% chance of inheriting pathogenic or susceptible biallelic ACAD enzyme and probably developing SCADD related clinical finding, the clinical symptoms involved privation of energy and reduction sugar level in blood, and eventually if not treatment, prevalence in newborn 1:40,000[4,27].

2-7-Dienoyl-CoA Reductase Enzyme Deficiency

Causative by decrease of 2,4-Dienoyl-CoA Reductase enzyme activity, it have a vital role in oxidation of fatty acid, the accident of this disorders implicate privation energy, depression of blood sugar and clinical problems in some organs and eventually fatal death[21,23].

III. ORGANIC ACID DISORDERS

The organic acids plays a vital role in the metabolism of proteins, lipids and carbohydrate, and any deficiency of the enzymes in metabolic pathways causes accumulation of organic acids and then appearance in the blood and urine, and the toxicity of this compound causes many disorders inside the body[7,28]

3-1-Isovaleric Aciduria disorders

The Isovaleric Aciduria disease considered one of the type organic acid disorders, and who is associated with lack of Isovaleric Acid-CoA Dehydrogenase enzyme, which is accountable to analyze the aminoacid leucine, the diagnosis was further confirm by genetic examination of the molecules. Some patients have been diagnosed with a homozygous missense variant p. G250A has limited effect on hydrogen bonds, this disorder related with many clinical symptoms like malnutrition, waste of energy and coma, prevalence is 1:250,000 in newborn[29,30].

3-2-Propionic Aciduria Disorders

It is the most common disease for this type of metabolic disorders, as a result of depression of Propionyl-CoA Carboxylase enzyme activity, this enzyme play an vital role in metabolism pathway of many essential amino acids, 55 different mutations have been identified in Propionyl-CoA Carboxylase gene in patients worldwide. And a duplication of A271C has been identified as the most common mutation, and the symptoms for this disorders involve seizure, vomiting and fluid loss, it is widespread in newborn very high with rate 1:3000[29,31].

3-3-Glutaric Aciduria Class I Disease

Any defect in activity of Glutaryl-CoA Dehydrogenase enzyme causes Glutaric Aciduria disorders, which has an important role in analysis some amino acids, The GCDH gene located on chromosome 19p13 which contain 11 exon and spans about 7kb genomic DNA. This gene codes an enzyme called acyl dehydrogenase. The main feature of this disease in babies halt enlargement and brain bleeding, spread is 1:30,000 [32,33].

3-4-Methylmalonic Aciduria Disorders

The Methylmalonic Aciduria disorders correlated with any defect in VB12 metabolism or as a result from deficiency in methylmalonic-CoA Mutase enzyme activity, Autosomally recessive, MethyImalonic Aciduria is hereditary. Prenatal diagnosis clinically possible for families with MUT, MMAB, or MMAA mutation using molecular genetic testing after proband mutation has been detected, the symptoms of this disorders implicate damage in brain cell and increase ammonia levels in blood, propagation is 1:450,000 in children[33,34].

3-5-Deficiency of 3-Methylcrotonyl-CoA Carboxylase enzyme

Caused by decrease in 3-Methylcrotonyl-CoA Carboxylase enzyme concentration, this enzyme catalase the main step in metabolism pathway of amino acid leucin, A link between genotype and phenotype has not been identified as yet. Unlike other amino acid degradation disorders which are cofactor-responsive, the clinical signs of 3-Methylcrotonyl-CoA Carboxylase include state of sleepiness and deferred development, availability about 1: 46,000 in babies[3,35].

3-6-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

Caused by deficiency of the 3-Hydroxy-3-Methylglutaryl-CoA Lyase enzyme, that plays a part in the amino acid leucine breakdown, the symptoms involving vomiting, it’s a rare disruption[28,32].

3-8-Deficiency of Maternal Vitamin B12 Disorders

This disorder as a result of a deficiency of vitamin B12 in both mom and babies, even during pregnancy period, Accumulating experience with DNA based study has shown that it is not only possible to recognize fetal chromosome aneuploidies, this disorders diagnosis with underdevelopment of growth and muscle hypotension, there are unusual disorders in babies[29,36].

3-9-Methylbutyryl-CoA Dehydrogenase Deficiency

Occur by absence of 2-Methylbutyryl-CoA dehydrogenase enzyme, which have a minor role in amino acid isolucin metabolism, The diagnosis of this disease was confirmed by demonstration of compound heterozygosity for a missense mutation in 2-Methylbutyryl-CoA Dehydrogenase gene, the clinical symptoms involve brain obstruction and privation of motor competencies, its scare disease[33,37].

IV. CARBOHYDRATE DISORDERS

The carbohydrate which is a main source for energy production in the cells, most of carbohydrate is simple and another is complex decompose to
monosaccharide, and there are many types of monosaccharide and each of them have specific metabolic pathway, and any change in enzymatic activity in this pathways causes different disorders[38,39,40].

4-1-Galactosemia Disorders

The galactosemia disease Considered one of most genetic disorders that correlated with metabolism pathway of galactose, babies with this disorder lack the ability to convert the glucose o glucose and energy production, the main causes of this disease are any defect of three enzymes in Lelior pathway, then accumulation occur for a number of metabolic product like galactitol and that causes damage in brain cell and liver, happened in babies in the rate 1:44,000[38,41,42].

4-2-Glucose-6-Phosphate Dehydrogenase Deficiency

It’s another type of carbohydrate disorders take place in new born, and associated with defect in Glucose-6-Phosphate Dehydrogenase enzyme, the patient lack the ability to remove the oxidant compound from the cell and hence destruction of RBC in the body, the main symptoms involve severe anemia and have high prevalence in babies 1:3000[40,43].

V. OTHER DISORDERS

5-1-Hemoglobinopathies Disease

Among the hemoglobinopathies, sickle cell disease (SCD) and -thalassemia have the most impact on morbidity and mortality, affecting millions worldwide.1 Both are prototypical Mendelian single gene disorders affecting the -globin (HBB) gene the hemoglobinopathies. Caused by a number of mutation in gene of hemoglobin, there are a variety of related disease in this umbrella, many of which revolve around the failure to distribute oxygen effectively across the body, the coexistence differs but in certain area of Arab World it may go as far as 1:700[44,45].

5-2-Cystic Fibrosis Disorder

Cystic fibrosis disease is one of the autosomal recessive disorder caused by any mutations occur in the cystic fibrosis transmembrane regulator gene, the position of this gene on the q arm of chromosome 7. This disorders have strong effect on many organs like Lung and digestive system, the body develops dense, oily mucus that can block the pancreas and clog the lung, cystic fibrosis may be life-threatening and individuals with this disease appear to have a reduced life expectancy than normal life span[46,47].

5-3-Congenital Adrenal Hyperplasia Disease

Congenital adrenal hyperplasia (CAH) designate to a aggregation of autosomal recessive disorders which damage cortisol synthesis pathway, therefor the higher production of corticotropin release CRH hormone and adrenocorticotropic (ACTH) hormone, from the pituitary glands and hypothalamus, continually contribute to the augmentation and buildup of numerous steroid compound proximal to block, this disorders associated with deficiency in 21-Hydroxylase enzyme, which has an important role in cortisol and aldosterone synthesis, symptoms involve early adolescence, stunted development and misalignment of gender, which may contribute to death at the most extreme Prevalence in newborn about 1:2500[48,49].

5-4-Congenital Hypothyrodism Disorder

Congenital hypothyroidism is the most common neonatal metabolic disorder and results in severe neurodevelopmental impairment and infertility if untreated, this disease is mainly caused by an abnormal thyroid gland secretion or occur mutation in the hormone receptor gene developed to support the thyroid gland function, symptoms involve impaired growth and development, and untreated intellectual retardation, affects children 1:4500[6,46,50].

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