



ISSN: 2395-7476
IJHS 2015; 1(3): 47-49
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www.homesciencejournal.com
Received: 22-07-2015
Accepted: 24-08-2015

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Inborn Errors of Metabolism: A review

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Abstract

The number of patients have increased over time. Erbe. W.R. 1975 reported that interest in this group of disorders stems from the likelihood that they may result in serious neurologic impairment, from the possibility that they will respond to therapy with folates, and from their potential contribution to an understanding of human folate metabolism. Moreover the patients 'disorders remain undiagnosed leading to increased mortality. Doctors often consider IUGR or LBW to be the major cause of neonates' death. But the real cause is failure to administer the correct amino acid /s' formulae to the neonates. Mother's milk is intolerable in some cases to such neonates. Also the infants who survive have to sustain on artificial feeds specially designed to serve such disorders, the increased cost of such packaged feeds being borne by their parents via imports. India especially suffers from such a problem tremendously as there is no provision for such feeds being manufactured by medical companies inland.

Keywords: inborn errors, metabolism, IUGR or LBW

Introduction

The inborn errors of metabolism were genetically determined and inherited as a recessive Mendelian character. The genetically determined mechanism underlying each disease is the absence of an enzyme or active compound required for a particular metabolic process. Many types of inborn errors of metabolism described in man and can be treated by eliminating certain substances from the diet or by adding some specific nutrients to the diet. Some of them described below are:

- Sickle Cell Anemia
- Cooley's Anemia
- Albinism
- Alkaptonuria
- Cystinosis
- Hartnup Disease
- Maple Syrup Disease
- Prolinemia
- Hydroxyprolinemia
- Methylmalonic Aciduria
- Hereditary Fructose Intolerance
- Galactosemia
- Wilson's Disease
- Histidinemia
- Phenylketonuria

Haemoglobin S (Sickle cell anemia)

The red blood cells of certain individuals possess the peculiar property of undergoing a reversible alteration in shape due to changes in the partial pressure of oxygen within the cell. When oxygen tension is lowered these cells change from their normal biconcave form to elongated filamentous or crescentic forms. Patients with this, show a moderate anemia and little or no spleen enlargement. Examination during or shortly after such a hemolytic crisis will show an icteric tinge to the sclera, increased pallor of the lips and mucous membranes and frequent liver enlargement. In severe cases enlargement of heart with hemic murmurs occur precipitated by an acute infection. Death may occur of increased severity.

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Cooley's anemia or Mediterranean Anemia

It is a hemolytic anemia associated with a hereditary defect in the synthesis of haemoglobin. The blood contains excess amounts of fetal Hb (HbF) which is destroyed rapidly. The onset is indicated by severe and progressive anemia early in infancy. Anemia is not present at birth. There is a gradual decrease in production of fetal Haemoglobin. Splenomegaly is also progressive and if no supportive transfusion therapy is given leading to death.

Albinism

It is a disorder of amino acid metabolism. It is a hereditary disorder characterized by a decrease or absence of melanin formation. The absence of melanin in albinism could result either from a congenital absence of the melanocyte or from a metabolic defect in pigment formation within the cell. Albinism occurs because of a hereditary lack of tyrosinase within the melanocyte of the skin.

Alkaptanuria

It is the inborn error of aromatic acid metabolism in which diagnosis rests on the classical triad of arthritis, pigmentation of cartilages, and darkening of urine representing a metabolic block in the oxidation of homogentisic acid. In both, the alkaptanuric liver and kidney there is a marked deficiency of homogentisic oxidase but all other enzymes are present in normal amounts. Homogentisic acid accumulates in the blood and is excreted in the urine. The homogentisic acid is at least in part responsible for the deposition of pigment and ochronosis in the tissues.

Cystinosis (Cysteine Storage Disease)

It is the metabolic disorder in which cysteine crystals are deposited in many tissues and organs throughout the body. It is accompanied by a generalized aminoaciduria in which all amino acids are considerably increased in the urine. Renal functions are impaired and these patients die at an early age with all of the manifestations of acute renal failure.

Hartnup Disease

It is a hereditary disease characterized by the presence of 'Hereditary pellagra-like rash with temporary cerebellar ataxia, constant aminoaciduria and other biochemical features.' The clinical features vary with patient and the season of the year. Scaly red rashes appear affecting the exposed areas of the body. They walk with an unsteady gait and wide base, nystagmus and double vision that are sometimes present. Defects in the absorption of amino acids are also observed in the small intestine. The most prominent effect of this is excessive loss of amino acids is a decreased supply of tryptophan for endogenous formation of nicotinamide resulting in pellagra-like symptoms. Oral administration of nicotinamide (40- 200 mg of nicotinic acid daily) will cure the dermatitis. Avoidance of excessive exposure to sunlight is also helpful.

Maple Syrup Urine Disease (MSUD)

It is characterized by cerebral symptoms and an odor of the urine similar to that of the maple syrup. All affected infants show clinical symptoms in the first few days of life. There is a difficulty in feeding, an absence of the neuro reflex and the development of irregular and jerky respirations. Signs of spasticity and coma are also seen. There is rapid deterioration in the condition of the patient and the infants die within a few weeks or months. MSUD is caused by an autosomal recessive

gene and by a block in the oxidative decarboxylation of the keto- acids of the branched chain amino acids- Valine, Leucine, and Isoleucine. This causes accumulation of the branched chain amino acids and the corresponding alpha keto acids as well as allow isoleucine. Treatment should be initiated by giving an amino acid mixture free of Valine, Leucine and isoleucine and there should be a prompt reduction in the branched chain amino acids in the blood and improvement in the clinical symptoms. As the infant grows older, gelatin can be used as a protein source as it contains low concentrations of branched amino acids. The mixture of essential amino acids deficient in gelatin can be added to it like tryptophan and methionine. In addition a balanced diet and gluten- free flour's products are used to make diet more nutritionally adequate and add variety in the diet.

Prolinemia

This results from defects in proline and hydroxyproline catabolism that are extremely rare. It is characterized by elevated plasma levels and the urinary excretion of large quantities of proline, hydroxyproline and serine. The patients are afflicted with severe mental retardation.

Hydroxyprolinemia

It reflects the absence of activity of the enzyme catalyzing conversion of 4- hydroxyl L- proline. The clinical findings include severe mental retardation, elevated plasma hydroxyproline levels and the urinary excretion of abnormal quantities of hydroxyproline and hydroxyproline peptides.

Methylmalonic Aciduria

Two forms exist. One responds to vitamin B-12 and the other does not. In the B-12 unresponsive disease, the enzyme methyl- malonyl- CoA isomerase is defective. The defect in the B 12 responsive form of methyl- malonic Aciduria thus appears to be the inability to form 5' deoxyadenosyl- cobalamin from normal levels of the vitamin.

Hereditary Fructose Intolerance (Aldolase Deficiency)

It is characterized by severe hypoglycemia and vomiting shortly after ingestion of fructose. Prolonged periods of fructose ingestion in children lead to growth failure to vomiting, jaundice, hepatomegaly, albuminuria, and aminoaciduria and finally to cachexia and death. Patient develops a strong distaste to fruits and sweets. The chronic picture for this syndrome is only encountered in children. Hepatic fructose- 1- phosphatase (Aldolase B) is deficient. Fructose- 1 – phosphatase accumulates in the liver cell after fructose loading and leads to acute hypoglycemia by blocking glycogenolysis.

Galactosemia

There is a hereditary condition resulting from a disturbance of galactose metabolism. Infants with this condition usually appear to be normal at birth, but after milk feeding, they vomit, become lethargic, fail to gain weight and show hepatomegaly. Prolonged jaundice during the neonatal period is a common finding and ascites and edema may develop. In severe cases, death occurs owing to malnutrition and wasting in the first few months of life. Those who survive are usually malnourished and dwarfed, with cataracts and mental retardation occurring in some instances. Very early therapy may reverse or completely prevent the cataract formation. There is also an accumulation of galactose- 1- phosphate occurs in the red cells of the patients. This metabolite has also

been identified in the brain, kidney, liver, lens and heart of galactosemia patients. Treatments of these patients include rigid exclusion of lactose and galactose from the diet.

Wilson's Disease

It is a rare hereditary disorder of copper metabolism. About 50% of the ingested copper is absorbed as compared with 2-5% in normal persons. There is also a defect in ceruloplasmin formation. Hence, the copper absorbed is deposited in various tissues such as brain, liver, kidney and in Descemet's membrane in the eye. These organs may be damaged by some poisoning of certain enzymes by copper or by cellular necrosis followed by fibrosis in the brain. The biochemical signs are present from birth but, the clinical signs do not appear until adolescence. There are clinical types-

- **Hepatic type**-There is progressive hepatic cirrhosis of a coarse nodular type, leading gradually to portal hypertension and eventually to hepatic failure. Juvenile cirrhosis should always suggest the possibility of Wilson's disease with jaundice preceding it. It is sometimes hemolytic in type.
- **Cerebral type**-The cardinal manifestations are neurologic abnormalities arising from dysfunction of the lenticular region of the brain. Necrosis and sclerosis of the corpus structures cause basal ganglion syndromes in adolescence. Loss of emotional control is also witnessed.
- **Hepatic and Cerebral types**-Both hepatic and cerebral signs may be present in some cases.

Histidinemia

It is an inherited disorder of Histidine metabolism. In addition to increased levels of Histidine in the blood and urine, there is also increased excretion of imidazole pyruvic acid. Speech development may be retarded. The metabolic block in Histidinemia is considered to be inadequate activity of liver histidase. The alternative pathway of Histidine metabolism involving transamination to form imidazole pyruvic acid would then be favoured and the excess imidazole pyruvic acid would be excreted in the urine. Imidazole acetic acid and imidazole lactic acid have also been detected in the urine of histidinemic patients.

Phenylketonuria (PKU)

It is a hereditary condition characterized by mental retardation and the presence of phenyl pyruvic acid. It is due to genetic deficiency of phenylalanine hydroxylase enzyme essential for conversion of phenylalanine to tyrosine. As a result of this deficiency the cerebrospinal fluid and the blood contain amounts of phenylalanine and its pyruvate, lactate and acetate derivatives greatly in excess of normal. Damage to brain may occur be severe and irreversible unless treatment is instituted at an early stage. Mental deficiency is the most common clinical feature but convulsions, tremor, rhythmic rocking of the body and posturing of the hands in front of the eyes also occur. Skin lesions such as dryness, roughness and eczema are common. If effective treatment is begun in time i.e. within the first few weeks or months of life, the clinical features can be prevented or if already present may get ameliorated. Mental state is affected in case the treatment is delayed in first few months of life. Elevations of serum phenylalanine can be effectively controlled by reducing the content of this amino acid in the diet. However, complete elimination is not recommended since phenylalanine must be supplied in the diet for normal physical growth along with a nutritionally adequate diet.

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