

## **Inborn Errors of Metabolism**

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### **Definition**

Inborn Errors of Metabolism are defects in the mechanisms of the body which break down specific parts of food into chemicals the body is able to use. Resulting in the buildup of toxins in the body.

### **Introduction**

Inborn Errors of Metabolism (IEM) are present at birth and persist throughout life. They result from a failure in the chemical changes that are metabolism. They often occur in members of the same family. Parents of affected individuals are often related. The genes that cause IEM are autosomal recessive.

Thousands of molecules in each cell of the body are capable of reactions with other molecules in the cell. Special proteins called enzymes speed up these reactions. Each enzyme speeds up the rate of a specific type of reaction. A single gene made up of DNA controls the production of each enzyme. Specific arrangements of the DNA correspond to specific amino acids. This genetic code determines the order in which amino acids are put together to form proteins in the body. A change in the arrangement of DNA within the gene can result in a protein or enzyme that is not able to carry out its function. The result is a change in the ability of the cell to complete a particular reaction resulting in a metabolic block. The areas of the cell these errors occur determine the severity of the consequences of the break down in metabolism. For example if the error occurs in critical areas of energy production, the cell will die. Or if the block in metabolism is in a less sensitive area the cell survives with the defect. These errors are recessive and can be passed on from generation to generation undiscovered until the defective gene is present in both parents. Inborn Errors of Metabolism can occur in Carbohydrate Metabolism (Galactosemia, Glycogen Storage Disease, Hereditary Fructose intolerance, and others), and Protein Metabolism (Phenylketonuria, Methylmalonic Acidemia, Homocystinuria, Tyrosinemia). Protein Metabolism Errors result in an amino acid that cannot be broken down. They accumulate in the body and cause toxic effects in brain development and physical growth. The Protein Inborn Errors of Metabolism will be the focus of the remainder of this discussion.

### **PHENYLKETONURIA (PKU)**

The total absence of Phenylalanine hydroxylase, an enzyme, activity results in elevated Phenylalanine, an amino acid, in the blood. The accumulation of phenylalanine frequently results in Mental Retardation. Incidents in the USA are about 1/16,000 births.

### **Diagnosis**

Clinical symptoms of PKU are usually absent in the newborn therefore early diagnosis depends on detecting a high plasma Phenylalanine level. This test is performed by taking a small amount of blood, usually from the heel, after the infant has been drinking formula or breast milk for 48 hours. Prenatal diagnosis is now available in the majority of families with a history of PKU.

### **Prevention and Treatment**

Strict adherence to a Low Phenylalanine diet that is nutritionally adequate in calories, fat, essential amino acids, vitamins and minerals is key to the prevention of the mental retardation that results from the accumulation of Phenylalanine levels. Phenylalanine must be included in limited amounts as it is an essential amino acid and is needed for protein building. The diet includes low-phenylalanine or phenylalanine free protein substitutes, natural

foods to provide limited phenylalanine and low-protein products. Several commercial formulas and supplements are available such as Lofenelac & Phenyl-Free by Mead Johnson; Analog XP, Maxamaid XP, and Maxamum XP by Ross. A Registered Dietitian will need to do a complete nutritional assessment including nutrient intake, anthropometric measurements, biochemical data and physical examination. The individual diet prescription must be evaluated frequently to ensure that protein, phenylalanine, calories, vitamins and mineral requirements are met. Nutritional progress is monitored by monthly serum phenylalanine determinations. Intellectual development within the normal range has been achieved in PKU patients with early diagnose and early treatment. Investigators have found a small but significant defect in intellectual ability of PKU children compared to unaffected family members. The low-phenylalanine diet is fairly easy to maintain during infancy and early childhood, it becomes very difficult for the adolescent and adult because of lower phenylalanine needs and slower growth rate. Termination of the low-phenylalanine diet in most people with PKU has been accompanied by deterioration in intellectual and neuro-psychological functioning. agrophobia, anxiety and depression are other complications.

### **METHYLMALONIC ACIDEMIA**

Methylmalonic Acidemia (MMA) was first recognized in critically ill infants with profound metabolic ketoacidosis (a build up of acid in the body) who excreted large amounts of methylmalonic acid. MMA is an array of different biochemical and clinical disturbances caused by defective conversion of methylmalonyl-CoA to succinyl-CoA. One disturbance involves Vitamin B12 and is responsive to Vitamin B12. A clinical picture of metabolic acidosis characterizes Methylmalonic academia. In addition to metabolic acidosis there may be excessive amounts of ammonia in the blood, hypoglycemia, and the presence of methylmalonic acid in the serum, urine and cerebrospinal fluid. There is usually a serious illness early in life, typically with vomiting, acidosis, dehydration, and lethargy leading to coma and death unless there is intervention. In less serious cases growth is poor, and there is a reduction in all-cellular elements of the blood.

#### **Treatment**

There are several defects that cause methylmalonic academia, and the biochemical defect determines the outcome for the person. Death or severe impairment is usually the outcome. People who are responsive to vitamin B12 usually have the best outcome. Emergency treatment during infancy includes peritoneal dialysis, eliminating protein in the diet and supplying carbohydrate to treat hypoglycemia is often required. Long-term management requires frequent monitoring of serum and plasma amino acids and restricting amino acids in the diet to prevent either excess or deficiency. Protein synthesis requires all essential amino acid be present in adequate amounts. Both excess and deficiency can lead to increased excretion of methylmalonic acid. Anemia and Congestive heart failure are frequent complications.

### **HOMOCYSTINURIA**

The metabolic pathway that converts methionine to cystathionine and then to cysteine is blocked. This occurs in approximately 1 in 200,000 live births.

#### **Diagnosis**

Homocystine (an amino acid) is excreted in large amounts in the urine. Some clinical signs are extreme near sightedness, osteoporosis, scoliosis, high arched palate, mental retardation, psychiatric disturbances, vascular occlusions, fair brittle hair, thin skin and others. Homocystine, not normally detected in the plasma, may be as high as 2 mM. Plasma cystine is low. Clinical symptoms are not consistent with about half of people with Ectopia Lentis (displacement of the lens of the eye), who have normal intelligence. The diagnosis is often not suspected until repeated thromboembolic episodes (the blocking of a blood vessel caused by a blood clot). Prenatal diagnosis is done by measuring cystathionine synthase activity in cultured aminocytes.

## Prevention and Treatment

Restriction of dietary methionine, the addition of cystine to the diet, and administration of B6 (pyridoxine) has been shown to reverse biochemical abnormalities in over ½ of patients. Most deaths are a result of Thromboembolic Episodes.

Folic acid deficiency may occur and will need to be corrected before B6 response is observed. Some instances require treatment with vitamin B12. There are several commercial methionine restricted formulas available such as Methionaid, and Analog Xmet. Frequent measurement of plasma and urinary concentration of methionine and homocystine are recommended until it is determined whether the biochemical abnormalities are altered by B6 administration. Some people who respond to B6 administration may still need methionine restriction. Adequate methionine and cystine for growth and tissue maintenance must be provided.

## Emergency Situations – What can go wrong?

Thromboembolic episodes are the primary emergency situations that arise.

## TYROSINEMIA

The constant urinary excretion of large quantities of tyrosine and tyrosine metabolites. Several conditions resulting from different defects produce these biochemical features.

Tyrosinemia Type I- Hereditary tyrosinemia was first recognized by Baber in 1956. It is autosomal recessive disorder that produces severe and usually fatal liver disease in infants and children. Screening world wide reveals a range of incidence in 1 in 50,000 to 1 in 100,000 in most populations except for a region in Quebec Canada, which has a prevalence of 1 in 685. Symptoms appear in infancy and include vomiting, jaundice, failure to thrive and abdominal enlargement. A cabbage like odor is usually present. Death from liver failure occurs in 90% of patients by 1 year of age.

Tyrosinemia Type II or Richner-Hanhart syndrome- The most frequent findings are corneal ulcers and skin lesions. The painful lesions can hinder mobility and mental retardations occur in about half the patients, some of who have microcephaly and convulsions. Tyrosine is the only amino acid increased in the urine in this type of Tyrosinemia other amino acids are normal. Tyrosinemia Type II is rare with fewer than 20 cases reported.

Transient neonatal tyrosinemia.—This type of Tyrosinemia is usually without symptoms although anorexia, lethargy, prolonged jaundice and reduced motor activity have been reported, in addition to intellectual deficits. It is most common in the immature infant who is receiving a high protein diet and an inadequate amount of ascorbic acid. An enzyme necessary in the breaking down of tyrosine is inhibited. The enzyme activity can be restored by ascorbic acid. Treatment is to reduce protein intake and administer 100 mg of ascorbic acid.

### Prevention and Treatment of Tyrosinemia Type I and Type II

Diagnosis during the prenatal state has been accomplished for Type I Tyrosinemia by analyzing amniotic fluid between 15 and 21 weeks gestation. Prenatal diagnosis of tyrosinemia type II is not available.

Acute Tyrosinemia type I is treatable by the dietary restriction of tyrosine, phenylalanine, and methionine. In this manner plasma elevations of these amino acids are lowered reducing the excretion of tyrosine metabolites and correcting the renal tubular abnormalities. Treatment does not reverse the liver disease nor alter the progression to liver failure. Treatment of Tyrosinemia Type II by restriction of tyrosine and phenylalanine effectively lowers tyrosine concentration in body fluids, and symptoms resolve promptly.

**References**

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