CHAPTER 34

Nutrition Support in Metabolic Disorders

Introduction

In 1990 over 4900 metabolic disorders were catalogued. About 250 of these have a defined biochemical basis. These disorders result from variation in the structure of enzymes or protein molecules. The amino acid sequences of enzymes, which are proteins, and their quantity are decided by genes. About 30% of our population is heterozygous for common alleles, as suggested by the extent of normal variation in genes. Relatively rare traits, which result in disease, are produced by mutations of genes. The frequency of occurrence of mutant genes varies in populations. For example, maple syrup urine disease (MSUD) occurs in about one in 250,000 newborns worldwide, but in an inbred Mennonite population, it occurs one in 176.

Genetic disorders can affect the metabolism of proteins, carbohydrates, lipids, pyrimidines, minerals and vitamins, depending on the metabolic pathway that is affected.

To prevent irreversible changes, such as brain damage, in infants, population-wide nonselective screening of newborns has been instituted for PKU, MSUD, galactosemia, homocystinuria and tyrosinemia in UK and USA. In these disorders, speed in diagnosis and treatment is of the utmost importance.

Metabolic Disorders Benefited by Nutrition Support

In metabolic disorders accumulation, excess production or lack of normal substrates and metabolic products, leads to toxic symptoms. In many of these, appropriate changes in the dietary supply helps to alleviate the problem.

Identifying the affected persons before irreversible changes have occurred is a very important step in optimum management of these disorders. Analysis of the amniotic fluid cells in the sixteenth to eighteenth weeks of gestation can help to detect a number of genetic disorders. Such search for genetic disease is done when there is a family history of inherited disease. Such tests help to prevent future error such as congenital cataracts in galactosemia by removing lactose from mother's diet. Many metabolic disorders can be detected by analysis of blood, urine, etc. of susceptible infants.

It must be noted that persons suffering from metabolic disorders benefit from nutrition support, when it is given promptly after detection. In this chapter, only a few disorders will be discussed to illustrate that early nutrition support can prevent irreversible, severe pathogenic problem.

Right approaches to therapy of metabolic disorders are discussed here. Selection of the method depends on how the disease occurs. Several methods may be used in sequence or at the same time, depending on the case.

1. *Correct the basic imbalance in metabolic reactions.*
   For example, in **phenylketonuria (PKU)**, which occurs due to phenylalanine hydroxylase deficiency, intake of phenylalanine is limited and tyrosine is supplemented.
2. *The excretion of accumulated metabolic products, which are overproduced, is enhanced.*
   In **gout**, the blood uric acid levels are lowered by blocking renal reabsorption with use of drugs. Then the tissue deposits of uric acid are mobilised for use.
3. *Alternate metabolic pathways are provided to reduce accumulation of toxic precursors in blocked reaction.* For example, in urea cycle defects, the accumulated ammonia is decreased by using nitrogen to form phenylacetyl glutamine from glutamine by giving curative amounts of phenylacetic acid.
4. *To reduce overproduction of reaction products by use of inhibitors.* Thus in gout, overproduction of uric acid is inhibited by use of allopurinol.
5. *Products of blocked pathways are provided.* Administration of pancreatic enzymes, when the normal secretion is blocked, helps to correct the digestive defect in cystic fibrosis.
6. *Altered enzyme proteins are stabilised.* Appropriate intake of the co-factor vitamin B_6 in homocystinuria or thaimine in MSUD increases intracellular coenzymes of these vitamins and hence the specific activity of the related enzymes.
7. *Deficient cofactors are replaced.* Appropriate intake of specific vitamin precursor cures a number of vitamin dependent disorders, which occur due to blocks in production of their coenzyme.
8. *Genetic counseling to limit the frequency of inherited diseases.* Genetic counseling can prevent marriages between high-risk individuals and thus reduce the birth of affected progeny.

The main component of treating inherited disorders is nutrition management. In addition to dietary restrictions, some amount of chemically tailored foods need to be used to correct imbalances in metabolic relationships.

Metabolic Disorders Involving Amino Acids

Amino acids are the building blocks of proteins. They have many functions in the body. Metabolic disorders related to amino acids can occur due to defects in the way they are metabolised or their entry into the cells. As these disorders lead to symptoms early in life, newborns are screened for them routinely in some countries.

Phenyl ketonuria (PKU) was discovered in 1933. Prevention of mental retardation caused by it, is a classic example of diet therapy.

Of the amino acid disorders, **phenyl ketonuria (PKU)** will be discussed, as it is one of the few causes of mental handicap for which reasonably effective treatment is available.

In classic PKU, the activity of the enzyme phenylalanine hydroxylase is less than 1 per cent of normal. This enzyme is present in the liver and converts excess phenylalanine to tyrosine, another amino acid which is eliminated from the body. In 1 to 3 per cent cases with defective hydroxylation, there is deficiency of the cofactor tetrahydrobiopterin, and in this rare condition, the brain damage is not prevented by dietary treatment.

Phenylalanine is an essential amino acid, which needs to be provided through food, as it cannot be synthesized in the human body.

Phenylketonuria (PKU) is a group of inherited disorders of phenylalanine metabolism. It is caused by impaired phenylalanine activity. The symptoms occur at 3 to 6 months of age. These include developmental delay, microcephaly, abnormal electroencephalogram, eczema, musty odour and hyperactivity.

In some countries (UK, USA) neonates are screened between 6^{th} to 14^{th} day after birth for PKU. If diagnosed for PKU, treatment must be started immediately, to minimise the deleterious effects of the disease.

Treatment involves intake of controlled low-phenylalanine diet and regular monitoring of the blood phenylalanine concentrations. Phenylalanine is an essential amino acid. If the amount in the diet is insufficient, brain damage will occur. Hence the essential requirement must be ingested each day, a part of the daily requirement being given with each meal. The synthetic protein substitute for PKU must contain all the other essential amino acids needed. In addition, tyrosine becomes essential due to the metabolic block. The recommended intake of all other nutrients is similar to that of other infants.

The practical management of the PKU diet is very important. The levels of phenylalanine in the blood should be monitored on specimens taken 3.5 to 4 hours after a feed or main meal, using a micromethod (Guthrie), so that a capillary sample can be used. The suggested frequency of checking is weekly during the first few months for infants, every two weeks after weaning to toddler age; every 3 – 4 weeks in preschool age and 4 weekly thereafter up to teens; after that, it may be every 2 – 3 months or less. Young children are likely sometimes to pilfer food or suffer from infections. At such times the blood levels of phenylalanine needs to be checked and monitored.

During infection, when a child is likely to eat poorly, a high-energy drink must be fed to avoid breakdown of tissues, which may elevate phenylalanine level.

Human milk has lower phenylalanine content than cow's milk. Hence time-controlled breast-feeding can be judiciously combined with use of protein substitute for a newly diagnosed infant.

The sweetener, aspartame (nutrasweet/other brand name) contains phenylalanine and should not be fed to phenylketonuric patients of any age. Manufactured foods containing these sweeteners also need to be avoided from the PKU diet.

A lady suffering from PKU, who wishes to have a child, must be advised to stick to low – phenylalanine diet, much before conception and continue it through pregnancy. The blood levels must be strictly controlled. Strict monitoring of the diet is essential to ensure adequate supply of energy, phenylalanine and tyrosine and other nutrients to ensure appropriate growth of the fetus.

When a mother with phenylketonuria, takes normal diet during pregnancy, her child has a high probability of suffering from severe congenital abnormalities such as mental retardation, microcephaly and heart defects.

Maple Syrup Urine Disease (MSUD) is a group of inherited disorders of the metabolism of the branched-chain amino acids leucine, isoleucine and valine. Impairment of the branched-chain alpha-keto acid dehydragenase occurs due to several different mutations.

At birth infants with MSUD appear normal and well. But after intake of a protein-containing feed, in severe cases seizures, aponea (suspension of breathing), occurs. If not treated death occurs within ten days of birth.

Hence it is urgent to screen susceptible newborns for MSUD, diagnose it and start appropriate feeding promptly within the first week of life. This may consist of orogastric feeding of branched-chain aminoacid-free protein and energy source, which should be started as soon as possible after diagnosis is made. The aim is to initiate anobolism in the infant and prevent accumulation of neurotoxic branched-chain aminoacids.

For patients with 15% or more enzyme activity, protein intake of upto 1.5 g/kg/day may be sufficient.

The long-term diet therapy for MSUD involves maintenance of plasma concentrations of the branched-chain amino acids within specified limits, to permit maximum intellectual development and provide all other nutrients for optimal growth.

The nutrition support is achieved by use of special medical foods and natural foods.

Galactosemia

Lactose is the principal carbohydrate and energy source for infants and young children. Galactose is found only as a component of lactose in natural foods and has a central metabolic role in human nutrition.

Galactose is formed by hydrolysis of lactose by lactase in the intestine.

Galactose must be converted in the liver to glucose before it is used; this occurs through three enzymatic steps. (Fig. 34.1).

Galactosemia may occur due to deficient function of any of three enzymes (galactokinase, galactose-1-phosphate uridyl transferase or UDP galacto-4-epimerase)

Deficiency of galactokinase results in only cataracts.

Galactosemia due to deficiency of galactose-1-P-transferase leads to accumulation of galactose-1-P with progressive damage to the central nervous system, liver and renal tubule, if galactose restriction is not started in the first few days of life. In most of the untreated infants, who survive, retarded mental and physical growth occurs.

Diagnosis of galctosemia is made by measuring galactose-1-P transferase activity in erythrocytes. Recently a rapid ancillary method has been developed for prenatal diagnosis of galactosemia. In this method, the amniotic fluid of a fetus is analysed for elevated level of galactitol by GC/MS, which indicates impaired transferase activity.

Nutrition support aims to prevent or improve symptoms and at the same time provide adequate energy and other nutrients to ensure normal growth and development of the infant. Treatment consists of the removal of all sources of lactose and galactose from the diet. It should be started from the first week of life.

Human milk contains 6 to 8 per cent lactose, cow's milk 4 to 5 per cent lactose and infant formulas 7 per cent lactose. These milks must be replaced by a formula low in galactose. Soya protein isolate formulas have been found to be suitable, as it contains only 1.4 mg galactose per 100ml. in oligosaccharide forms which are not hydrolysed in the human intestine

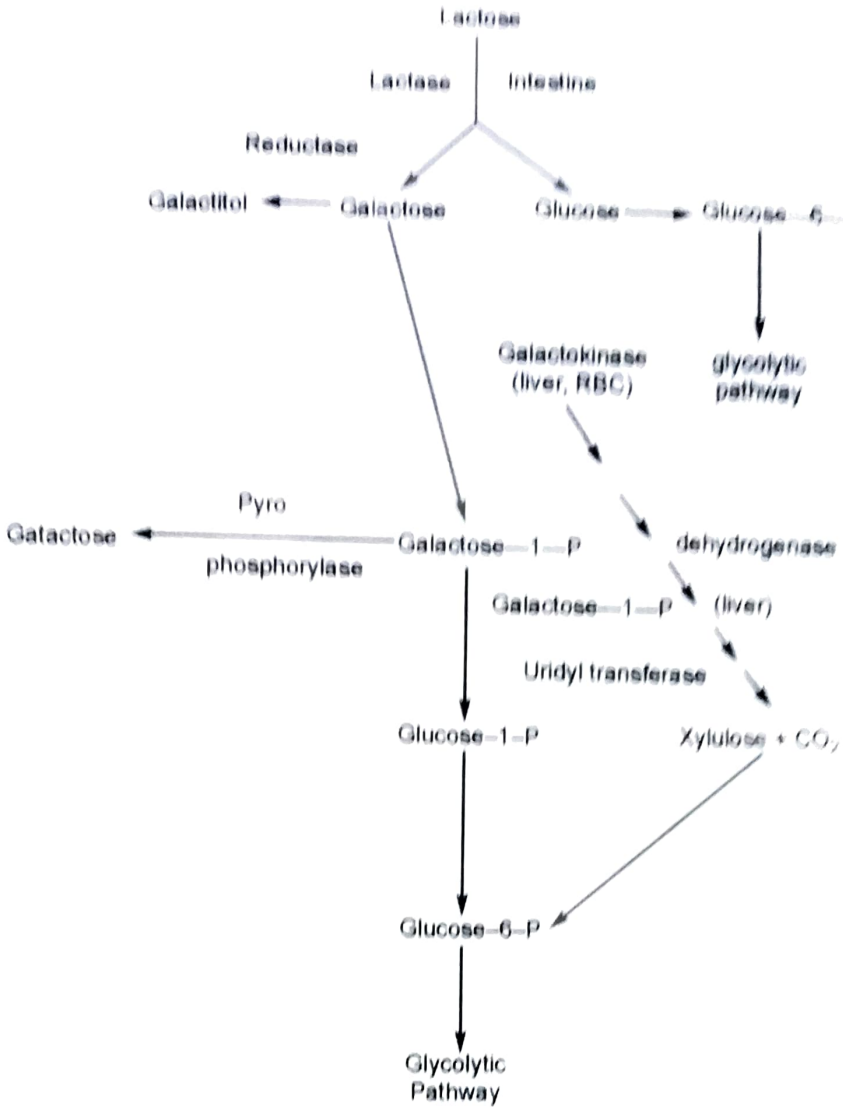

Figure 34.1 Metabolic blocks in galactose metabolism that lead to galactosemia. Genetic disorders of catalyssed reactions are indicated by hatched bars

As the child grows, solid foods are added to the diet, after proper scrutiny to avoid lactose containing foods. Even fermented dairy products and aged cheeses must be excluded from the diet, as the conversion of lactose to lactic acid is not complete in these.

Foods allowed - in galactose restricted diets are – cooked rice, chapaties, millet breads made without milk addition, home-made cakes, puddings, pasta, all dals, legumes, nuts and seeds.

Fats – Oils, nuts, shortenings.

Sugar Beverages – carbonated drinks, fruit juices other than apple, grape, pear and papaya.

Meat, fish, poultry – all primary products, not prepared ones, which contain milk or milk products.

Soups – clear soups, dal soups, vegetable soups made with vegetables allowed.

Vegetables – asparagus, beets, cabbage, cauliflower, celery, corn, cucumbers, brinjal, lettuce, ladies' finger, potatoes, spinach and yams.

Miscellaneous foods – Popcorn, pure sugar candy, jelly or marmalade, sugar, corn syrup, pickles, pure spices and seasoning, molasses, honey.