Maple syrup urine disease (msud) types

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The characteristic smell of maple syrup in urine of affected patients gave the disease its name following its discovery in the early 1954 by J. H. Menkes and his colleagues. A group of researchers led by Dancis in 1960, discovered that the metabolic block in MSUD is caused by an insufficient supply of a digestive enzyme that catalyses the breakdown of three branched-chain amino acids, leucine, isoleucine and valine. The deficient enzyme was defined in 1978, and is now known as branched-chain alpha-keto acid dehydrogenase complex (BCKD) (Podebrad, F. et al., 1999).

In affected patients, the three branched-chain amino acids and their by-products known as ketoacids build up in the urine, blood and other body tissues. Normally, a baby born with MSUD undergo severe acidosis, where it abnormally develops high levels of acid in the blood, during the first weeks of life, followed by seizures and coma due to the swelling of brain tissue, and ultimately leads to death (Scriver, C. R. & Kaufman, S., 2001).

MSUD is caused by a mutation in one of the four genes which code for the proteins making up the branched-chain alpha-keto acid dehydrogenase

complex (BCKD). The BCKD complex is necessary to break down branched chain amino acids (BCAA) into smaller molecules. The BCAAs namely are valine, isoleucine and leucine (Morton, D. H., 2002).

As explained in the book, The Metabolic and Molecular Bases of Inherited Disease the BCKD complex is a multimeric enzyme composed of three catalytic subunits. The E1 portion of the complex is a thiamine pyrophosphate (TPP)-dependent decarboxylase with a subunit structure of Î±2Î²2. The E2 portion is a transacylase composed of 24 lipoic acid-containing polypeptides. The E3 portion is a homodimeric flavoprotein (King, 2012).

The activity of BCKD is regulated by two additional subunits, a kinase and a phosphatase that reversibly phosphorylate/dephosphorylate the complex respectively. The phosphorylated enzyme is inactive. There are four genes responsible for the regulation of this enzyme, which are E1Î± gene (branched chain keto acid dehydrogenase E1, alpha polypeptide), E1Î² gene (branched chain keto acid dehydrogenase E1, beta polypeptide), E2 gene (dihydrolipoamide branched chain transacylase E2) and E3 gene (dihydrolipoamide dehydrogenase) (Mitsubuchi, H. et al., 2005). Mutations in any of the above four genes will inactivate or reduce the functioning of the BCKD complex and the breakdown of branched chain amino acids, thus causing BCAAs and the acid by-products to accumulate in the body, causing symptoms. The symptoms of this disease include urine that smells like maple syrup, avoiding food or feeding difficulties, coma, high pitched crying, lethargy, poor weight gain, seizures and vomiting (Park, H. D. et al., 2011).

The first (reversible) step is catalyzed by BCAA aminotransferases; the corresponding BCKAs are produced from the BCAAs leucine, isoleucine, and valine â‘ . In the second (irreversible) step, BCKAs are catalyzed by BCKDH, which is a rate-limiting enzyme in this pathway â‘¡. The transamination of BCAAs and decarboxylation of BCKAs form CoA compounds (Mitsubuchi, H. et al., 2005).

MSUD is classified by the pattern of signs and symptoms defined by the amount and type of enzyme activity in the body. Researchers have distinguished 5 subtypes as in Table 1 (Jinno, Y. et al, 1984).

Clinical forms of MSUD and its explanations.

The most common and severe form is the classical type. Symptoms develop soon after birth, usually within the first week of life. Enzyme activity is less than two percent (2%). The characteristic smell of urine emerges towards the latter days. If untreated, classical MSUD can be fatal.

Intermediate

This is a very rare form of the disease, with an enzyme activity of up to eight percent (8%).

Intermittent

This form of the disease being the second most common type. The affected babies will initially show normal early development with normal intelligence and symptoms may become apparent in babies during the second year of infanthood. Enzyme activity is about 8-15% compared to normal levels. Symptoms may surface during illness or following rapid intake of protein rich

food. If duly untreated, intermittent MSUD could lead to slow development of the child, including mental retardation.

Thiamine-responsive

This is another rare form of the disease, where the enzyme activity can be increased by administering doses of thiamine hydrochloride and low protein diet to affected children.

E3-defficient

This is the rarest form of the disease, discovered recently, where a patient lacks the enzyme complex in whole along with a few supplementary enzyme complexes involved in protein digestion. No drugs or changed diet will help this type of MSUD.

Early diagnosis is critical in preventing neurological damage and death in infancy. There are several methods of diagnosis can be done such as genetic screening of newborns for the presence of mutated alleles in their genetic makeup. Besides, prenatal diagnosis can also be done by taking relative measurements of the branched-chain amino acids in the amniotic fluid of the mother’s placenta. After birth, the baby’s ear canal can be swabbed within 12-24 hours after birth, and the ear wax can then be tested for the odour of maple syrup (Prasanna, B. et al., 2011). In addition, blood tests, analyzing the level of different amino acids, and their relative percentage in blood and also be used in diagnosis. Other biomedical tests include measuring the concentration of organic acids in the baby’s blood for elevated levels of acid in baby’s urine (Hannon, W. H. et al., 2001).

The initial treatment of MSUD is the immediate reduction of branched-chain amino acids in the baby’s body tissues (Kevin, A. S., et al., 2009). Until the 1970s, dialysis of blood was used to reduce the levels of BCAA in blood. At present, more consistent methods have been developed, which include the administration of intravenous solutions of amino acids, without BCAAs, with glucose added to meet the body’s energy needs. Sometimes, insulin is added to aid amino acid processing. These infusions lower the blood BCAA level (Morton, D. H., 2002). In severe cases, MSUD could be treated by a liver transplantation.

The first successful dietary therapy for MSUD was introduced by S. E. Snydermand and his colleagues in 1964. The idea was to reduce the intake of food rich in branched chain amino acids (Morton, D. H., 2002). Dietary therapy is a lower-risk form of a long term treatment plan, providing efficient control of the disease. The diet should look to reduce the intake of branched chain amino acids as much as possible. Initially tests should be carried out to determine the metabolic activity of each of the 3 branched amino acids in relation to each other, to help plan the right diet. The intake if the amino acid leucine should be carefully controlled, as it is an essential amino acid, but excess undigested levels of leucine can be highly toxic. Supplements containing isoleucine and valine should be taken in appropriate doses in relation to the level of leucine in blood. Low levels of isoleucine and valine can cause severe rashes. It is crucial to include protein substitutes that provide non-branched amino acids. A supplement of vitamins, minerals and trace elements is also important. The diet should also contain ample calories; majorly form low-protein foods and protein free energy supplements.

The special dietary scheme would help patients to prevent continuing metabolic malfunctions, and also prevent associated damage to the nervous system, enabling the patient to have normal development throughout life. Children with MSUD should be advised constantly to strictly adhere to the low-protein diet. Hope is seen with gene therapy procedures, where the mutated sections of the alleles are replaced with the normal alleles using retrovirus carriers. This mechanism will completely cure the disease condition. However, gene therapy is still under study.