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DISEASE PROFILE OF MAPLE SYRUP URINE DISORDER: A MUTATION IN BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE COMPLEX FORMING GENES

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ABSTRACT

The name of maple syrup urine disease is derived from the sweet scent of patient's urine, this smell is somewhat like burned sugar (maple syrup), hence, "maple syrup urine disease". Occurrence of MSUD is 1 out of every 85000 infants in USA. The cause of MSUD is the unavailability of a branched chain alpha keto dehydrogenase which would have catalyzed the decarboxylation of alpha keto acids like Leucine, Isoleucine and Valine. These BCAAs (Branched Chain Amino Acids) accumulate alongwith their corresponding alpha keto acids and contribute to such phenotypic effects. Mutation in the genes coding for BCKDHA is responsible for such cause. Patients of MSUD are under the risk of poor metabolism when there is increased protein catabolism. Despite all the preventions and attention the infant may suffer from zinc deficiency, osteoporosis, spinal compression and myelopathy. The diagnosis of MSUD is recommended to be done right after birth. A blood test showing abnormal centralization of amino acids is enough to confirm MSUD. Treatment of this disease includes the intravenous organization ofamino acids which contain no BCAAs and making the use of accumulated amino acids.

KEYWORDS: The name of maple syrup Leucine, Valine.

INTRODUCTION

Maple syrup urine disease (MSUD) is also known as branched-chain ketoaciduria. MSUD is an autosomal recessive metabolic malfunction that affects amino acids that have branched chains. It is a form of organic acidemia. The condition goy its name from the distinctive sweet scent of a baby's urine. This disease is found 1 in 185,000 births across the globe. Maple syrup urine ailment (MSUD) is an aminoacido-pathy just like a catalyst deformity in the metabolic pathway of thelong chains of amino acidsclike leucine, isoleucine, and valine. Accumulation of these 3 amino acids and their relevant keto acids can cause encephalopathy and dynamic neuro-degeneration in babies that are not trated immediately. If there is no early diagnosis or dietary precautions taken, the symptoms do involve inadequate development academically and mentally. Subsequently, MSUD has been added to standard infant screening procedures. (Suryawan *et al*., 1998).

In 1954, a family lost 4 newborn children within 3 months of their births due to the neurodegenerative issue. The urine of these newborn children had a smell as of that of maple syrup. Therefore, this anomaly was called maple sugar urine disease. In 1960, Dancis et al observed that the enzymatic malfunction in MSUD was during the decarboxylation of the branched amino acids (Macmurdo & Grimmb,. 2015).

Early Signs

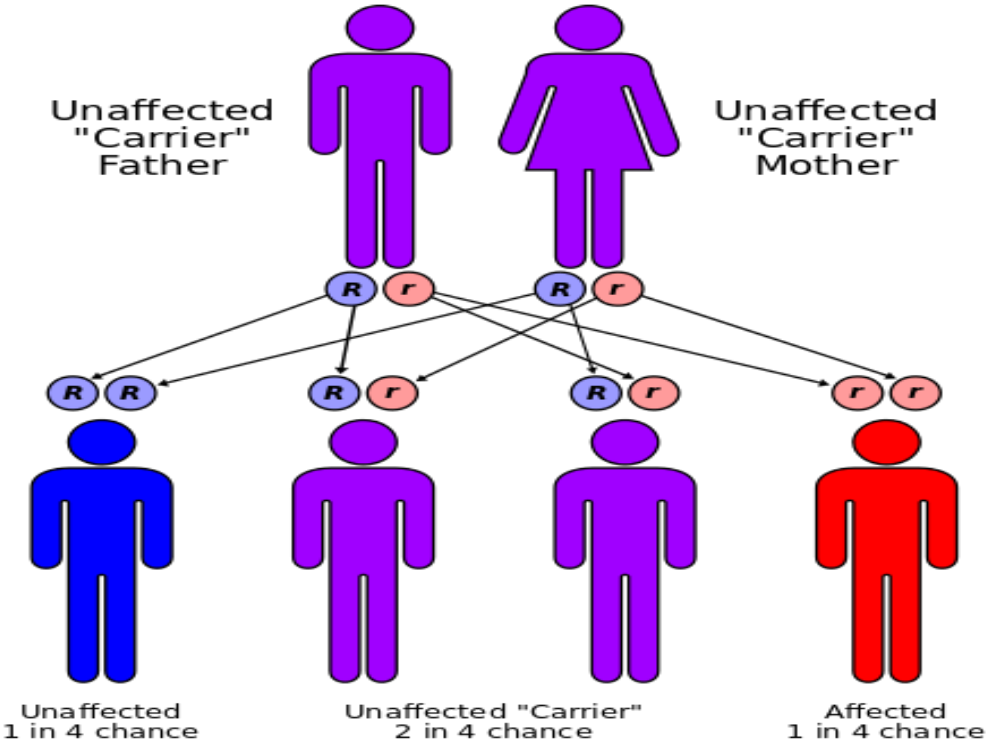
Maple syrup urine disease (MSUD) can be detected just twelve hours after birth, if left untreated, patients MSUD have a maple syrup scent in their urine; by 12-24 hours, there are high concentrations of leucine, isoleucine, and valine. By a few days ketonuria; by age four to five days, laziness, irregular sleeping patterns. By age seven to ten days, the patient has difficulty focusing on thing and other optical problems. Some other early signs of MSUD include exhaustion, loss of weight, loss of appetite, irregular sleep patterns, and high irritability (Clin *et al*. , 1997).

Causes

This disease is caused due to a mutation in the following genes: BCKDHB, BCKDHA, DLD, DBT. These four genes form a complex called the branched-chain alpha-keto acid dehydrogenase complex. This complex breaks down leucine, valine, and isoleucine. These amino acids are generally present in protein rich substances, for example, meat, nuts, beans and pulses. A change in these qualities makes the complex lose or reduction its capacity prompting collection of these amino acids in the

body and in a brief span, their aggregation harms the irreversibly.(Hou *et al.*, 2014).

Inheritance pattern of this disease is autosomal recessive which means it is present on an autosome and one copy of the gene must come from each parent in order for the disorder to be expressed. The parents of the child with an autosomal passive issue are transporters of one duplicate of the flawed quality, yet are generally not influenced by the confusion(Puliyanda & Harmon *et* al., 2002).



1. Inheritance Pattern of MSUD.

Symptoms

Maple syrup urine disease can lead to other medical issues such as; male pattern baldness, anorexia (not eating), acrodermatitis (an adolescence skin condition caused by infections, it would appear as a rash which is not irritated), and exhaustion. Repetitive diseases of Candida albicans, a yeast, are normally inside the mouth and the esophageal tract when patients are hospitalized. Additionally during hospitalization, doctors keep an eye out for intense pancreatitis. Intense pancreatitis is an irritation of the pancreas, some side effects can be a swollen and sensitized mid-region, sickness, retching, or fever (Verrey & Arch *et al.*, 2003) People affected by Maple syrup urine disease often have a lower IQ, nervousness, lack of concentration and are prone to Attention Deficit Hyperactivity Disorder (ADHD), and slow development. Discomfort and decreased motivation were observed in 86% of patients by the age of 36. Attention Deficit Hyperactivity Disorder was seen in 54% of patients who were on dietary precautions and in 82% of patients who had received a liver transplant. 70% of adult patients had developmental issues including tremors, dystonia, or both. Tremors are uncontrolled movements by limbs or joints. Dystonia are automatic muscle compressions that result in abnormal, uncomfortable positions or posture. Some initial symptoms characteristic of classic MSUD are a high-pitched cry, alternating episodes of hypertonia (muscle rigidity) and hypotonia (muscle limpness), poor appetite, weight loss, irritability, a distinctive maple sugar odor in earwax, sweat, and urine, weak sucking ability. In some cases, the ear wax of the patients can have a smell similar to maple syrup as well. Moreover, some other signs of this disease include lethargy, poor appetite, weight loss, irregular sleep patterns, alternating episodes of hypertonia (muscle rigidity) and hypotonia (muscle limpness), seizures, neurological deficiencies, developmental delays, feeding problems, poor growth (Menkes & Hurst *et al.*, 1954).

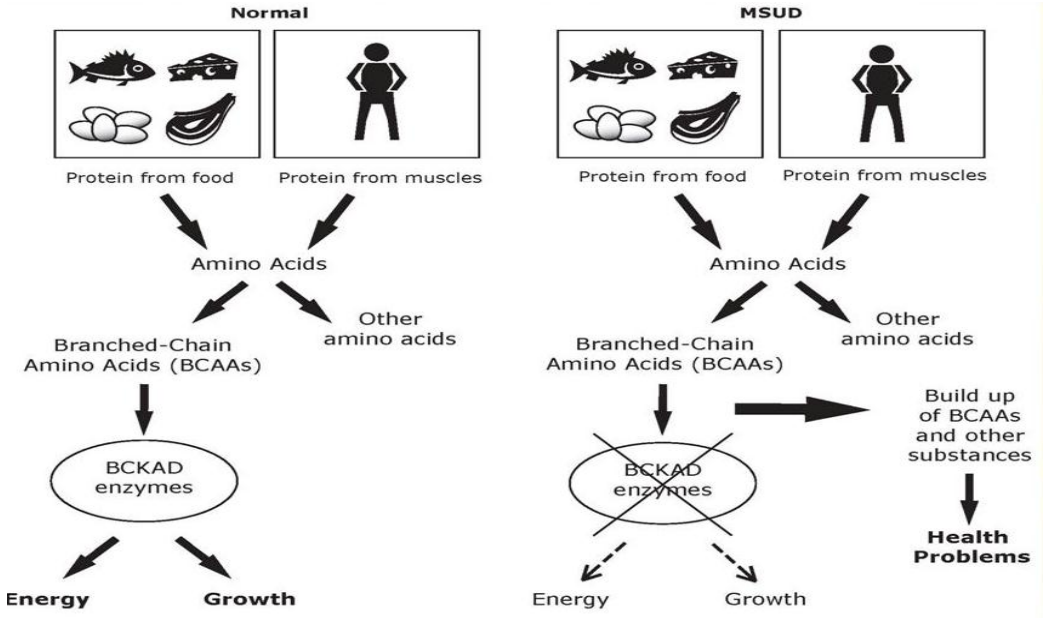


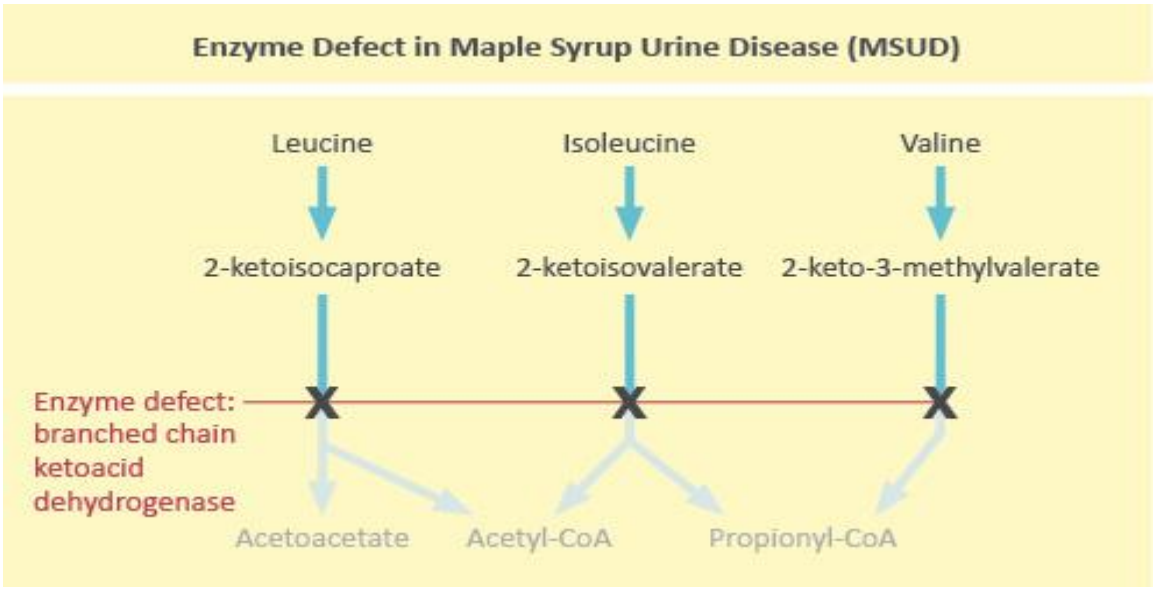
Fig. 2 Effects of MSUD on Energy and Growth.

Types

The National Organization for Rare Disorders (NORD) reports that Maple syrup urine disease happens at a similar rate in male and females. There are high chances of being affected by this disease if one of the parent's suffer from this disease. However, the intensity of the affects can be as such; 25 % possibility of getting two changed qualities and having Maple syrup urine disease, 50 % chance for accepting just a single damaged quality and being a bearer, 25 % shot of accepting one ordinary quality from every parent (Machius, Chuang, Wynn, Tomchick, Chuang *et al*., 2001).

In the case that someone has two ordinary qualities for the disease, they can not pass the infection to their offspring. However, when two guardians possess the recessive gene for MSUD, it is likely that one of their children will have the infection and others are unaffected. Each child has a 50 percent possibility of being affected. Maple syrup urine disease (MSUD) is a genetic disease which means it is passed down from one generation to another. Individuals with this condition cannot breakdown leucine, isoleucine, and valine. This causes the accumulation of these amino acids in the blood. MSUD can cause mental distress during times of physical stress; for example, during disease, and prolonged intervals without food. A few sorts of MSUD are mild or vary with various situations (Atwal, Macmurdo, Grimmb., 2015).

Maple Syrup Urine Disease is also called as: Branched Chain Ketonuria-I, BCKDC deficiency, Branched Chain Ketoaciduria, ranched-chain alpha-keto acid dehydrogenase deficiency.



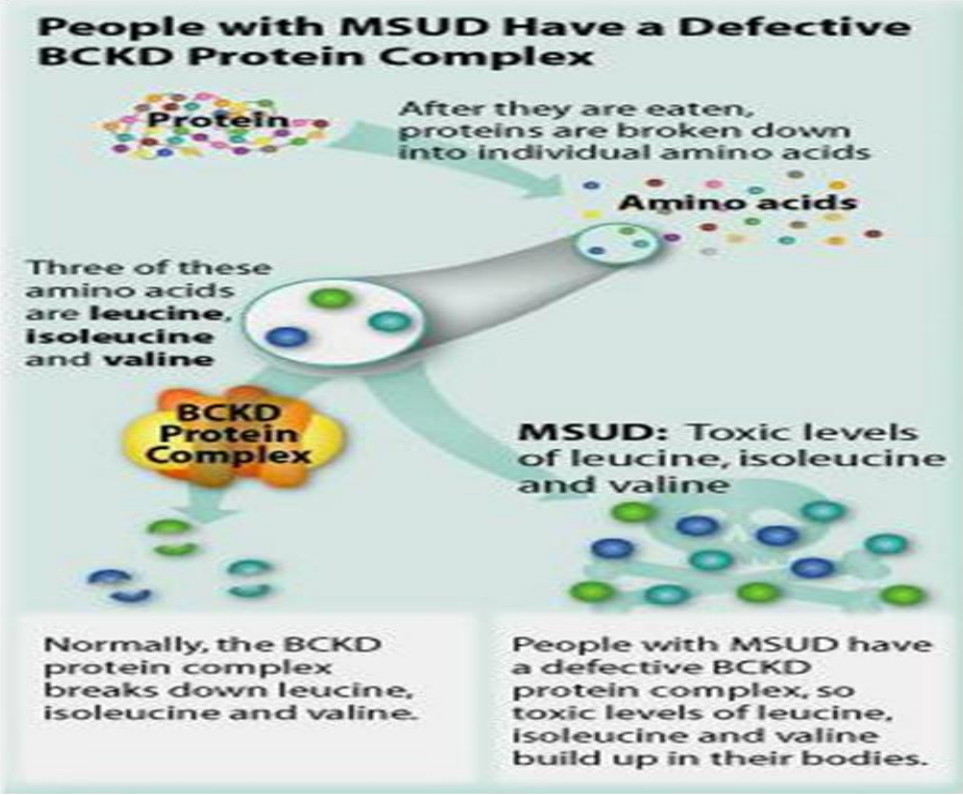
2. Enzyme Defects of MSUD.

Different types of MSUD depend on enzyme activity, severity, the age at which it occurs. There are four main types of MSUD: classic MSUD: this is the most fatal of all the types of MSUD. The signs of this disease begin with the initial intake of protein by a newborn. The enzymatic activity is critically low, intermediate MSUD: the age and symptoms of this type vary from individual to individual. However, the enzyme performs 3-8% of normal activity, intermittent MSUD: This type does not affect development or growth of the patient. Symptoms are not observed until the age of 1 or 2. The symptoms are more clearly seen when the body undergoes stress such as disease or stress, thiamine-responsive MSUD: this disease is controlled by the intake of large doses of thiamine/ Vitamin B. Although thiamine is beneficial, it must be taken in a certain limit (Novarino, Fishawy, Kayserili., 2012).

Diagnosis

An pediatrician may inquire as to whether a child is showing signs of MSUD If an infant has certain signs, an infant's specialist may suggest early treatment (starting at birth). In the possibility that an infant screening result for maple syrup urine disease (MSUD) was out of the typical range, retesting may be suggested. However, it should be kept in mind that an out-of-range screening result does not necessarily mean that a child has the disease. An out-of-range result may occur due to the blood test being performed too soon or too less blood was obtained for testing. If, a baby does have the condition, it is vital that you go to for a follow-up test. Since the unsafe impacts of untreated MSUD can happen very soon after birth, follow-up testing must be finished as quickly as time permits to figure out if or not an child has the condition (Hou, *et al.*, 2014).

Follow-up testing will include checking an infant's urine and blood tests for harmful measures of poisons and acids. Increased amounts of branched amino acids in the blood and increased ketones in the urine may mean that a child has MSUD. Distinguishing the nearness of MSUD during childbirth is basic to anticipating long harm. In situations when both parents are carrierss and their child's test is negative for MSUD, extra tests might be encouraged to affirm the discoveries and keep the onset of side effects (Atwal, Macmurdo, Grimmb., 2015).



1. Defective BCKD Complex.

At the point when side effects appear after the infant time frame, determination of MSUD can be made by a pee examination or blood test. A urine investigation can recognize a high centralization of keto acids, and a blood test can identify an abnormal state of amino acids. The finding of MSUD likewise can be affirmed with a chemical examination of white platelets or skin cells. On the off chance that you are worried that you may be a bearer of MSUD, hereditary testing can affirm on the off chance that you have one of the contorted qualities that cause the sickness. During pregnancy, doctors can utilize tests by chorionic villus inspecting (CVS) or amniocentesis to analyze your child (Zinnanti *et al.*, 2009).

Treatment

Beginning treatment includes lessening the levels of BCAAs in a child's blood. Usually, this includes intravenous (IV) organization of amino acids that do not contain BCAAs, joined with glucose for additional calories. The treatment will increase usage of existing leucine, isoleucine, and valin. It will lower BCAA level and provide essential proteins (Novarino, Fishawy, Kayserili *et al.*, 2012). The objective of the treatment plan is to give all protein and supplements required for proper development and growth. Hereditary testing can determine if either parent is a carrier of this genetic disorder. DNA testing can determine of the sickness is affecting the baby before birth. No matter how careful one is while monitoring a patient's diet, there still may be metabolic malfunctions. For best results treatment should begin as soon as possible so it can be tracked and unexpected mishaps can be prevented. If newborn child is determined to have MSUD, incite therapeutic treatment can dodge genuine medicinal issues and scholarly handicap. Beginning treatment includes decreasing the levels of BCAAs in your infant's blood. (Tuchman, Rapin, Neurol., 2002) Regularly, this includes intravenous (IV) organization of amino acids that don't contain BCAAs, joined with glucose for additional calories. The treatment will advance the use of existing leucine, isoleucine, and valine in the body. In the meantime it will decrease the BCAA level and give fundamental protein (Novarino, Fishawy, Kayserili., 2012).

Disease Management

Treatment of manifestations*:* Treatment comprises of dietary leucine limitation, controlled intake of isoleucine and valine, and regular testing. Hemodialysis/Hemofiltration to expel BCAAs from the extracellular compartment, Orthotropic liver transplantation, Prevention of primary manifestations, and evaluation of relatives at risk (Harris, Joshi, Jeoung, Obayashi., 2005).

CONCLUSION

Maple Syrup Urine Disease is a genetic disease which has various treatment and control methods depending on type and severity of malfunction. It is caused by the recessive genetic gene in one or both parents. This disease is mostly found in new born babies or infants. It causes mental retardation and developmental delays in extreme cases. Its milder types induce lethargy, moodiness, loss of appetite, sleeping irregularities, and metabolic anomalies. The most commonly observed symptoms of this disease, in all its types is the maple-syrup-like smell from urine, sweat and in some cases, ear wax.

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