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MAPLE SYRUP URINE DISEASE: NOWADAYS A PROBLEM IN HUMAN CIVILIZATION

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ABSTRACT

Maple syrup urine disease (MSUD) is a rare, inherited inborn error of metabolism caused by defects in the branched-chain α-keto acid dehydrogenase complex metabolic disorder. This results in elevations of the branched-chain amino acids (BCAAs) in plasma, α-ketoacids in urine, and production of the pathognomonic disease marker, alloisoleucine. This disease prevents the body from breaking down certain amino acids and these amino acids are what remain after the body digests protein from the food we eat. Special enzymes process amino acids so they can be used to maintain all of our body function. MSUD varies in brutality and the clinical spectrum is quite broad with five recognized clinical variants that have no known association with genotype. In MSUD, the body lacks an enzyme called BCKDC (branched-chain alpha-keto acid dehydrogenase complex). The BCKDC enzyme processes three important amino acids: leucine, isoleucine, and valine, also called BCAAs (branched-chain amino acids). This branched chain amino acids are found in foods rich in protein as for example meat, eggs, and milk. Untreated MSUD can cause significant physical and neurological problems. The classic presentation occurs in the neonatal period with developmental delay, failure to thrive, feeding difficulties, and maple syrup odor in the cerumen and urine, and can lead to irreversible neurological complications, including stereotypical movements, metabolic decomposition, and death if left untreated. Treatment of this terrible disease consists of dietary restriction of BCAAs and close metabolic monitoring. This article involves its presentation, screening and clinical diagnosis, treatment, and other relevant aspects pertaining to the care of patients.

Keywords: Maple syrup urine disease, BCKDC, alloisoleucine, BCAAs.

How to cite the article?

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1. INTRODUCTION

Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder affecting branched-chain amino acids. That's a type of organic acidemia. The condition gets its name from the distinctive sweet odour of affected infants' urine, particularly prior to diagnosis and during times of acute illness [1]. Other name of that disease is "Branched-chain Keto aciduria". This disease is characterized by disruption of the normal activity of the branched-chain α-keto acid dehydrogenase (BCKAD) complex, the second step in the catabolic pathway for the branched-chain amino acids (BCAAs) that include leucine, isoleucine, and valine.

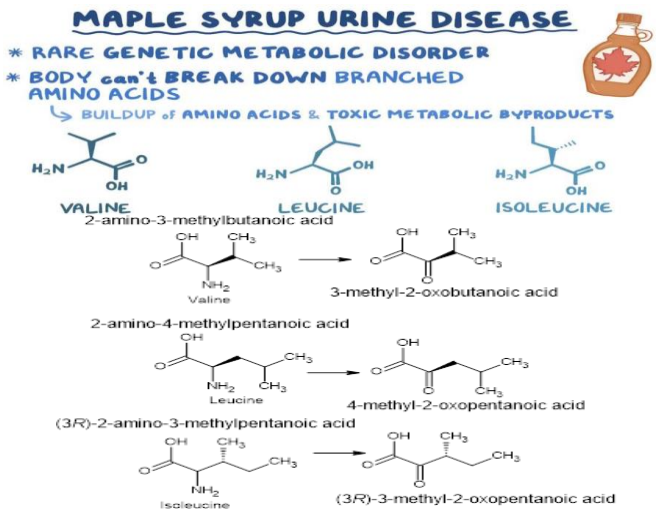

Figure 1: Amino acid to alpha keto acid formation [1]

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Pathogenic homozygous or compound heterozygous variants in *BCKDHA*, *BCKDHB*, *DBT*, or *DLD*, which form the catalytic subunits of BCKAD, can result in MSUD, which is characterized by neurological and developmental delay, encephalopathy, feeding problems, and a maple syrup odour to the urine. Patients with this disorder have elevations of branch chain ketoacids in the urine in addition to elevated BCAAs in the plasma. MSUD is amenable to treatment through dietary restriction of BCAAs, and with early treatment, patients typically have good clinical outcomes. MSUD is therefore included on the Recommended Uniform Screening Panel (RUSP), a list of actionable, early onset disorders for which screening is recommended for all new born in the United States. The use of tandem mass spectrometry (MS/MS) in new born screening (NBS) has helped facilitate early detection of and timely medical intervention for patients with MSUD, thus improving clinical outcomes in affected individuals [1].

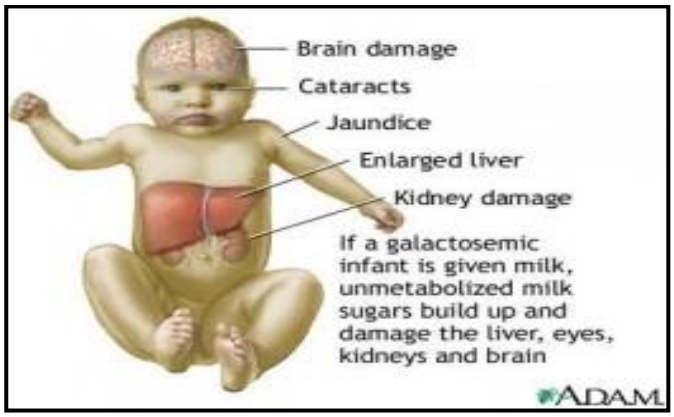

Figure 2: Babies affected with Maple Syrup Urine Disease [1]

Classification:

Maple syrup urine disease can be classified by its pattern of signs and symptoms, or by its genetic cause. The most common and severe form of this disease is the classic type, which appears soon after birth, and as long as it remains untreated, gives rise to progressive and unremitting symptoms. Sub-divisions of MSUD:

1. Classic MSUD,
2. Intermediate MSUD,
3. Intermittent MSUD,
4. Thiamine-responsive MSUD [2]

1. **Classic MSUD**- This is the most common and severe form of the condition. A person with this form has little, if any, enzyme activity - about 2 percent or less of normal activity. Symptoms are present in new born within a few days of birth. Onset is usually triggered when the infant's body begins to process protein from feedings.

2. **Intermediate MSUD**- This is a rare version of MSUD. Symptoms and age of onset vary greatly. People with this type of MSUD have a higher level of enzyme activity than classic MSUD -about 3 to 8 percent of normal activity.

3. **Intermittent MSUD**- This form doesn't interfere with normal physical and intellectual growth and development. Symptoms usually don't appear until a child is between 1 and 2 years of age. It's a milder form of classic MSUD. Individuals have significant enzyme activity-about 8 to 15 percent of normal activity. The initial reaction of the disease often occurs when the child experiences stress, illness, or an unusual increase in protein.

4. **Thiamine-responsive MSUD**- This rare form of the condition often improves with large doses of thiamine, or vitamin B-1. Symptoms usually occur after infancy. Even though thiamine can be beneficial, dietary restrictions also are necessary.

Signs and Symptoms:

The symptoms and severity of MSUD varies greatly from patient to patient and largely depends upon the amount of residual enzyme activity [3].

1. Classic MSUD:

Infants with classic MSUD will display subtle symptoms within the first 24–48 hours. Subtle symptoms include poor feeding, bottle or breast, lethargy, and irritability. The infant will then experience increased focal neurologic signs. These neurologic signs include athetoid, hypertonia, spasticity, and opisthotonus that lead to convulsions and coma. There may be temporary episodes of extreme hypotonia. In the end, central neurologic function fails with respiratory failure and death. As the early symptoms gradually emerge, a distinctive odor of maple syrup may be detected in cerumen, sweat, and urine. This is derived from one of the BCKA organic acids derived from its respective BCAA that accumulate as the disorder spirals out of control. Once the disorder has been treated and stabilized, there remains a life-long threat of sudden or gradual recurrent metabolic decompensation that results in a return of all the symptoms typical of untreated cases. Dietary intake of the BCAAs must be strictly controlled and monitored. An increasing catabolic rate can occur insidiously or may develop rapidly during any metabolic stress, including infection, even if very mild, psychological or physical stress, trauma or fasting. These episodes are characterized by emergence of the symptoms that are typical in an untreated case and are due to elevated BCAAs, especially leucine and the three associated BCKAs. Every episode can turn into a metabolic crisis and must be treated as vigorously as any episode in a newborn. Individuals with classic MSUD may show a degree of intellectual limitation and may develop a variety of behavioral issues including attention deficient hyperactivity disorder (ADHD), impulsivity, anxiety and/or depression and seizures. Additional complications with classic MSUD include generalized loss of bone mass (osteoporosis) that may predispose to fractures, and inflammation of the pancreas (pancreatitis). Some individuals may develop increased pressure in the skull (intracranial hypertension), which causes painful headaches that are sometimes associated with nausea and vomiting [2].

Figure 3: Difference between normal urine and maple syrup disease urine [2]

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2. Intermediate MSUD:

Intermediate MSUD has greater levels of residual enzyme activity than classic MSUD. The majority of children with intermediate MSUD are diagnosed between the ages of 5 months and 7 years. It is characterized with greater levels of residual enzyme activity than is seen with classic MSUD. Symptoms, when they occur may include lethargy, feeding problems, poor growth, ataxia, and acute metabolic crises that result in seizures, coma, brain damage, and, in rare cases, life-threatening neurological complications. The characteristic odor of maple syrup in the earwax, sweat and urine, is present. Some affected children may remain asymptomatic until later in life [2].

3. Intermittent MSUD:

Contrary to classic and intermediate MSUD, intermittent MSUD individuals will have normal growth and intellectual development. Symptoms of lethargy and characterized odour of maple syrup will occur when the individual experiences stress, does not eat, or develops an infection. Thiamine-response MSUD responds to treatment with thiamine (vitamin B1). Thiamine plays a role in the BCAA enzyme complex. The symptoms and clinical course of thiamine-responsive MSUD resembles intermediate MSUD and rarely presents in the newborn period. Affected infants respond to large doses of thiamine, which boosts residual enzyme activity. No individuals with thiamine-responsive MSUD have been treated solely with thiamine – most follow a combination of thiamine with a partially-restricted protein diet [2].

4. Thiamine-response MSUD:

Symptoms associated with thiamine-response MSUD are similar to intermediate MSUD. New born is rarely present with symptoms [2].

5. Later onset:

The symptoms of MSUD may also present later depending on the severity of the disease. Untreated in older individuals, and during times of metabolic crisis, symptoms of the condition include uncharacteristically inappropriate, extreme or erratic behaviour and moods, hallucinations, weight loss, anemia, diarrhea, vomiting, dehydration, lethargy, oscillating hypertonia and hypotonia, ataxia, sezures, hypoglycaemia, ketoacidosis, opisthotonus, pancreatitis [3], rapid neurological decline, and coma. Death from cerebral edema will likely occur if there is no treatment. Additionally, MSUD patients experience an abnormal course of diseases in simple infections that can lead to.

Causes:

Mutations in the following genes cause maple syrup urine disease:

- BCKDHA (Online Mendelian Inheritance in Man (OMIM): 608348)
- BCKDHB (Online Mendelian Inheritance in Man (OMIM): 248611)
- DBT (Online Mendelian Inheritance in Man (OMIM): 248610)
- DLD (Online Mendelian Inheritance in Man (OMIM): 238331)

These four genes produce proteins that work together as the branched-chain alpha-keto acid dehydrogenase complex. The complex is essential for breaking down the amino acids leucine, isoleucine, and valine. These are present in some quantity in almost all kinds of food, but in particular, protein-rich foods such as dairy products, meat, fish, soy, gluten, eggs, nuts, whole grains, seeds, avocados, algae, edible seaweed, beans, and pulses. Mutation in any of these genes reduces or eliminates the function of the enzyme complex, preventing the normal breakdown of isoleucine, leucine, and valine. As a result, these amino acids and their by-products build up in the body. Because high levels of these substances are toxic to the brain and other organs, this accumulation leads to the serious medical problems associated with maple syrup urine disease.

This condition has an autosomal recessive inheritance pattern, which means the defective gene is located on an autosome, and two copies of the gene – one from each parent – must be inherited to be affected by the disorder. The parents of a child with an autosomal recessive disorder are carriers of one copy of the defective gene, but are usually not affected by the disorder. The risk for two carrier parents to both pass the non-working gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier, like the parents, is 50% with each pregnancy. The chance for a child to receive working genes from both parents is 25%. The risk is the same for males and females. [3]

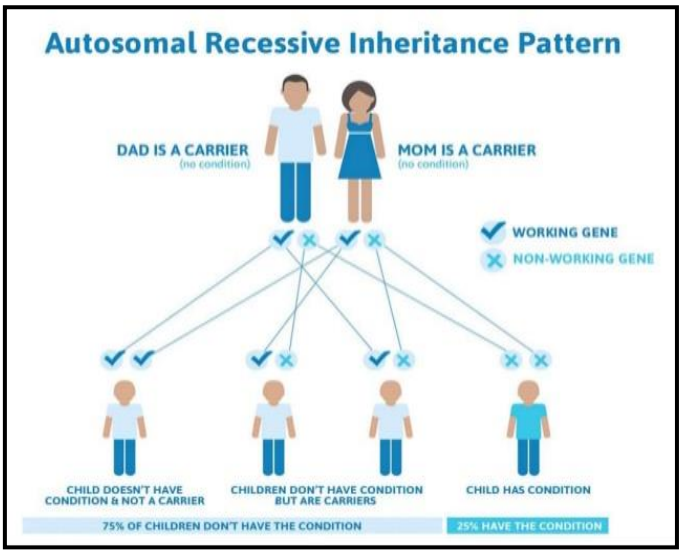

Figure 4: Autosomal recessive inheritance pattern of maple syrup urine disorder [3]

Pathophysiology:

MSUD is a metabolic disorder caused by decreased function of the BCKAD enzyme complex. Biallelic pathogenic variants in the catalytic components of BCKAD decrease its activity thereby increasing BCAA levels and causing toxicity within skeletal muscle and brain tissue [4-6]. BCAA catabolism is essential for normal physiological functions. The first step involves the conversion of leucine, isoleucine, and valine into their relevant α-ketoacids by branch-chain aminotransferase within the mitochondria as per picture. Unlike most other amino acid metabolism, the majority of this process does not take place in the liver but rather in skeletal muscle [7-9]. BCAAs can be found in protein-rich diets and are among the nine amino acids essential for human life, playing important roles in protein synthesis and function, cellular signaling, and glucose metabolism [10, 11]. During the second step in BCAA catabolism, the BCKAD complex initiates oxidative decarboxylation of α-ketoacids.

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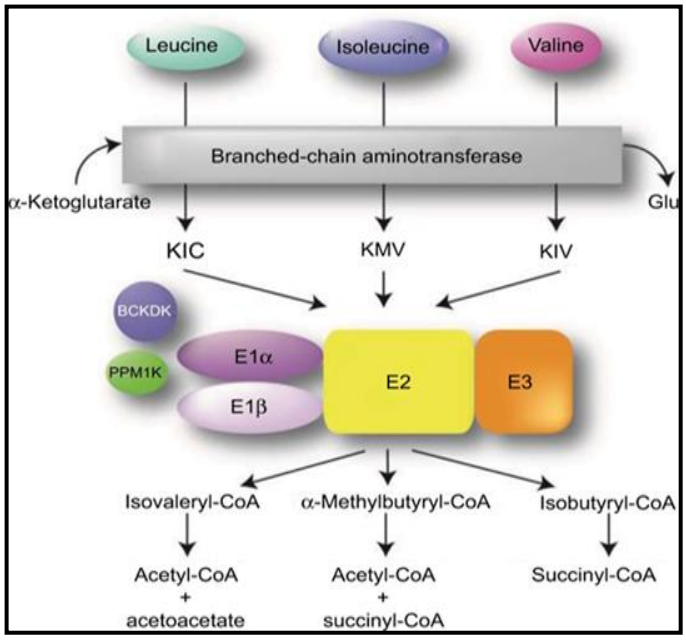

Figure 5: BCAA catabolic pathway: The BCAAs undergo transamination that is catalysed by the branched-chain aminotransferase (BCAT) and requires α-ketoglutarate, leading to the production of the α-ketoacids KIC, KMV, and KIV. These intermediates then undergo oxidative decarboxylation, catalyzed by the BCKAD complex. [10]

This process results in the conversion of α-ketoacids into acetoacetate, acetyl-CoA, and succinyl-CoA as illustrated as per picture. The BCKAD complex is made up of several components, including subunits E1α and E1β, E2, and E3. Increased BCAA levels within the body due to pathogenic defects in these components cause MSUD, leading to a variety of symptoms mentioned above, including dysfunction of the immune system, skeletal muscle, and central nervous system (CNS). The generation of various mouse models has been used to study MSUD and the effects of dietary BCAA restriction. In these models, as well as MSUD patients, excessive amounts of BCAAs build up and can cause severe tissue damage if left untreated [12]. Within the brain, BCAA metabolism functions to maintain glutamate levels. Glutamate serves as a neurotransmitter within the CNS [13, 14] and plays important roles in brain development and cognitive functions such as learning and memory. Disorders of BCAA metabolism can cause abnormalities in glutamate synthesis leading to various neurological problems in patients. Controlling plasma concentrations of BCAA levels is the key to preventing these symptoms. Furthermore, the accumulation of leucine is highly neurotoxic.

Elevated levels of leucine can affect water homeostasis within the subcortical grey matter causing swelling within the brain, alter nitrogen homeostasis further depleting glutamate levels, increase oxidative stress, and compete with other important amino acids within the CNS such as tyrosine, which is involved in protein signaling. In addition, there is evidence that α-ketoisocaproic acid, an intermediate in the metabolism of leucine, is a major neuro-toxin contributing to the encephalopathy syndrome. [7, 8]

Diagnosis:

Before the easy availability of plasma amino acid measurement, diagnosis was commonly based on suggestive symptoms and odor. Prior to diagnosis and during times of acute illness, Maple Syrup Urine disease was characterized by the distinctive sweet odor of affected infants' urine. Nowadays, affected individuals are often identified with characteristic elevations on plasma amino acids which do not have the characteristic odor. The compound responsible for the odor is sotolon. This disease is estimated to affect 1 out of 185,000 infants worldwide and its frequency increases with certain heritages. [1]

Newborn screening for maple syrup urine disease involves analyzing the blood of 1–2 day-old newborns through tandem mass spectrometry. It is a technique in instrumental analysis where two or more mass analyzers are coupled together using an additional reaction step to increase their abilities to analyze chemical samples. In order to determine whether the newborn has a high level of branched-chain amino acids, the blood concentration of leucine and isoleucine is measured relative to other amino acids. Once the newborn is 2–3 days old the blood concentration of branched-chain amino acids like leucine is greater than 1000 μmol/L and alternative screening methods are used. Instead, the newborn's urine is analyzed for levels of branched-chain alpha-hydroxyacids and alpha- ketoacids. [15-17]

SITUATION 1-

Abnormal Newborn Screening (NBS) result

- Newborn screening for MSUD is primarily based on the ratios of (leucine + isoleucine) to alanine and phenylalanine concentrations on dry blood spots.
- A positive screening value requires follow-up biochemical testing with quantitative plasma amino acid and alloisoleucine analyses.
- As leucine-isoleucine and hydroxyproline cannot be differentiated by mass spectrometry, neonates with isolated hydroxyprolinemia will screen positive for MSUD, but confirmatory amino acid analysis will show only increased hydroxyproline. This results to a false positive NBS result.
- Neonates and suspects who are suspected of having MSUD should never be challenged with higher protein intake during the diagnostic process. This process is considered dangerous.

SITUATION 2

A symptomatic individual with either atypical findings or untreated infantile onset MSUD

This may result due to:

1. NBS not performed.
2. False negative NBS result; or
3. Caregivers not compliant with recommended treatment following a positive NBS result

Supportive clinical and laboratory findings can include the following:

Clinical findings-

1. Untreated infant

- Maple syrup odor is detected in cerumen, 12 hours after birth.
- Signs of deepening encephalopathy including lethargy, apnea, stereotyped movements such as

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fencing and bicycling are evident by age four to five days.
- By age seven to ten days, coma and central respiratory failure may occur.

2. Untreated older individuals
- Anorexia
- Poor growth
- Acute hyperleucinemia
- Ketonuria and encephalopathy if stressed.
- Irritability
- Developmental delays later in infancy or childhood.

Laboratory findings-
- Ketonuria detected by standard urine test stripes.
- Absence of hypoglycemia and hyperammonemia.
- Elevated plasma concentrations of BCAAs and alloisoleucine
- Urinary excretion of BCKDs and branched chain alpha- ketoacids (BCKAs) in infants older than 48- 72 hours on an unrestricted diet.

Molecular genetic testing approaches-
Molecular testing is available for three biallelic pathogenic gene variants (A biallelic site is a specific locus in a genome that contains two observed alleles, counting the reference as one, and therefore allowing for one variant allele). These approaches include:
- BCKDHA gene: Encodes the E1-alpha subunit of the BCKAD enzyme complex (MSUD Type 1A).
- BCKDHB gene: Encodes the E1-beta subunit of the BCKAD enzyme complex (MSUD Type 1B).
- DBT gene: Encodes the E2 subunit of the BCKAD enzyme complex (MSUD Type 2). [18]

Genetic testing allows for accurate assessment of the deficient BCKAD subunit. It also allows for better understanding of the prognosis and genetic counseling of the family. This helps determine the individualized therapies. There are over 190 pathogenic variations in BCKAD enzyme subunits. All detected variants are homozygous or compound heterozygous.

Diagnostic strategies
- Adult with symptoms of MSUD:
- DNPH testing can be used to alpha-ketoacids in the urine.
- The most informative test is the identification of allo-isoleucine using plasma amino acid analysis.
- Branched-chain ketoacids and other organic acids can be detected using gas chromatography-mass spectrometry.

1. Newborn with signs and symptoms and a positive screening test for leucine, isoleucine, and valine or unexplained Ketonuria:
- If infants are older than 48 to 72 hours, screening tests such as DNPH and urine ketone test strips can be used.
- Plasma amino acid analysis to detect elevated BCAA and allo-isoleucine.
- Gas chromatography-mass spectrometry is used to analyze the urine for ketoacids.

2. Newborn with an affected sibling:
- If familial pathogenic variants are known, isolated blood from the umbilical cord can be used for a pathogenic variant detection by polymerase chain reaction (PCR), advanced sequencing, and melting analysis.
- If pathogenic variants are unknown, obtain blood from the umbilical cord to allow for pathogenic variant detection.

Prevention:
Since MSUD is an inherited disease, there is no method for preventing the manifestation of the pathology of MSUD in infants with two defective copies of the BCKD gene. However, genetic counselors may consult with couples to screen for the disease via DNA testing. DNA testing is also available to identify the disease in an unborn child in the womb. [14]

Treatment:
Effective treatment of maple syrup urine disease is required for addressing the nutritional needs and optimally managing acute metabolic decompensations. In the management/treatment of MSUD patients, the involvement of pediatric nutritionist and metabolic disease specialist are necessary. [15]

Medical nutritional therapy:
The nutritional therapy requires clinical confirmation and a positive newborn screening result. The mainstay of treatment remains the dietary restriction of branched-chain amino acids. These dietary modifications need to be maintained throughout life. The goals of nutritional therapy are as follows:
- Promote anabolism
- Prevent catabolism
- Maintain plasma BCAA levels within the required treatment ranges
- Evaluate thiamine responsiveness
- Promote normal growth and weight gain
- Preserve intellectual function
- Enable restriction of branched-chain amino acid in the diet, which helps reduce toxic metabolites

During respective life periods, the allowed amounts of dietary BCAA are titrated into the diet using biochemical lab values and growth measurements. Long-term treatment warrants accurate assessment of caloric needs, BCAA restriction, BCAA-free amino acid supplementation, and valine and isoleucine supplementation. Valine and isoleucine help promote anabolism. They are supplemented because they are low in content in medical nutrition. Leucine supplementation is usually not required because they are found in ample amounts in breast milk or formula. It is recommended that leucine concentrations are maintained between 75 to 300 micromol/L. Also, plasma leucine and isoleucine levels are recommended to be maintained between 200 to 400 micromol/L. In thiamine responsive patients, thiamine supplementation should be continued at a dose of 50 to 200 mg/day for four weeks. Thiamine should not be supplemented in patients diagnosed with the homozygous 1312T>A mutation or with mutations leading to less than 3% of BCKAD activity. Administration of sodium chloride may help maintain serum sodium concentrations and plasma osmolarity. It can help prevent the development of cerebral edema or fatal herniation.

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Treatment of acute metabolic decomposition:
Metabolic decompositions (i.e. plasma leucine >380 micromol/L) usually occur due to dietary non-compliance and infections. Dietary non-compliance raises the BCAA levels and rarely progresses to decompensation and encephalopathy.Decompensations arise more commonly in the first year of life and after the age of 15. The most common cause of hospitalization during acute decomposition is vomiting and viral gastroenteritis, viral bronchiolitis, sinusitis, neonatal encephalopathy, and urinary tract infections. During an illness, patients with higher residual BCKAD activity, face less severe elevations in leucine.

Management strategies in most severe cases include:

- Effectively treating the underlying stressor causing the metabolic crisis
- Restrict protein intake for 24 to 72 hours
- Provide ample caloric support
- Effectively treating the underlying stressor causing the metabolic crisis
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- Provide ample caloric support
- Effectively treating the underlying stressor causing the metabolic crisis
- Restrict protein intake for 24 to 72 hours
- Provide ample caloric support

Home therapy:
It is instructed to the providers to use a 2, 4-dinitrophenyl hydrazine reagent to detect high urine branched-chain ketoacids. This allows for the timely detection and home management of mild to moderate cases of acute metabolic decompensation. Restriction of dietary leucine, sick day formulas, and outpatient monitoring can be provided by experienced providers. Sick day protocols require a 120% increase in the intake of BCAA-free amino acid formula, fluid administration of 150 mL/kg, 50% to 100% decrease in leucine intake, and frequent small feedings.

In- hospital therapy:
Treatment strategies of in-hospital therapy include:

- Maintain sodium levels within the physiological range.
- Correct underlying acid-base disturbances.
- Avoid osmolarity fluctuations > 5 mosm/L per day and maintain urine output.
- Prevent and treat hypokalemia and hypophosphatemia associated with IV glucose and insulin therapy.
- Effectively treating the underlying stressor (e.g., fever, dehydration, infection, and inflammation).
- To control nausea and vomiting, antiemetic such as ondansetron should be administered.
- Reduction in leucine concentration at 750 micromol/L or more per 24 hrs. This reduction in leucine can be achieved via insulin and glucose infusions. Ideally, leucine levels should be maintained from 200 to 300 micromol/L. Upon clinical improvement, total parenteral nutrition can be used to reintroduce protein back into the diet (25%-50% of normal intake). This intake can be increased depending on the clinical situation over the next few days.

Isoleucine and valine should be supplemented at 20-120 mg/kg/day each. The intake of supplements is adjusted to maintain Sodium Phenyl butyrate is primarily used in the treatment of urea cycle disorders. NaPBA can also reduce branched-chain amino acid levels. It can be used in patients with intermediate MSUD. Hemodialysis and peritoneal dialysis can also be used to rapidly correct BCAA and ketoacids during an acute decompensation.

Orthotopic liver transplantation
Indications:

- Psychomotor disabilities
- Poor metabolic control
- Frequent metabolic decompensations
- A steady plasma concentration of 400-600 micromol/L.

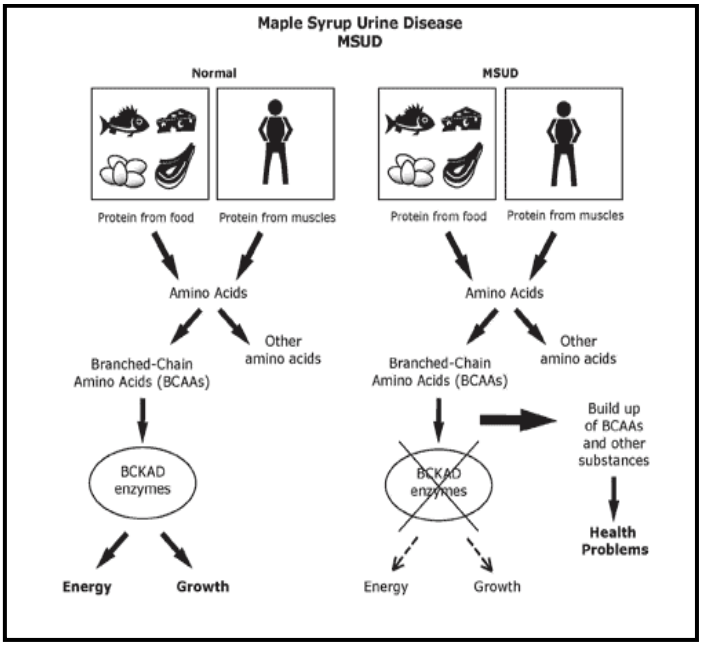

Figure 6: Role of Sodium Phenyl butyrate (NaPBA) [15]

As liver is responsible for expressing 10% of BCKAD activity, it is recommended for classic MSUD patients who are difficult to manage. Post-transplantation, the residual activity of BCKAD can rise to that of mild MSUD levels. Therefore, transplantation tends to reduce the requirement of dietary restrictions and episodes of metabolic decomposation. It also does not reverse previously inflicted brain damage, cognitive dysfunction, and psychiatric illnesses.

Management in pregnancy:
Control of metabolism is vital during pregnancy of women with MSUD. To prevent detrimental abnormalities in development of the embryo or fetus, dietary adjustments should be made and plasma amino acid concentrations of the mother should be observed carefully and frequently [4].Maintaining BCAA levels between 100 and 300 micromol/L is said to be compatible with normal infant delivery. At the time of delivery, referral to a metabolic center must be made. This is because the post-partum period is deemed dangerous for the mother. Events such as labor stress, internal blood sequestration, and uterine involution can act as a source of metabolic decompensation. Therefore, extra measures must be taken to counteract catabolism during the post-partum period. [15]

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Management of other MSUD Complications

Cerebral Edema

- Administer furosemide (0.5 to 1.0 mg/kg)
- Infusion of mannitol (0.5 to 1.0 g/kg) followed by hypertonic saline (3%-5%)
- Elevating the head can reduce the risk of developing cerebral edema.

Cerebral Herniation

- Induce hyperventilation with the help of a face mask or endotracheal tube.
- Infuse mannitol and hypertonic saline.
- Transfer the patient immediately to a pediatric/neonatal intensive care unit.

Acute Pancreatitis

During an acute metabolic decompensation episode, a patient may develop symptoms such as epigastric pain, mid-back pain, anorexia, and vomiting. This could lead to acute pancreatitis and immediately order serum levels for lipase and amylase. Treatment is usually supportive, and the patient's nutritional needs can be managed with the use of special parenteral solutions.

Neuropsychiatric Illnesses

Adult and adolescent patients are at an increased risk of developing anxiety, depression, and ADHD. These can be treated by prescribing standard anti-depressants and psycho-stimulant drugs.

Secondary Complications

Surgical procedures and trauma care should be planned in coordination with a metabolic specialist.

Prognosis:

If left untreated, MSUD will lead to death due to central neurological function failure and respiratory failure. Early detection, diet low in branched-chain amino acids, and close monitoring of blood chemistry can lead to a good prognosis with little or no abnormal developments [12]. Plasma leucine concentrations are known to affect neurocognitive outcomes. Classic MSUD in school-aged patients has shown high performance than IQ. While 61% of adult patients with MSUD can live and interact independently, about 55% of patients still require psychological and psychiatric care. A delayed diagnosis of more than 7 to 14 days of classic MSUD can result in irreversible learning disability and cerebral palsy.

Epidemiology:

Maple syrup urine disease (MSUD) is an extremely rare and inherited metabolic disease. Its prevalence in the United States population is approximately 1 newborn out of 180,000 live births. However, in populations where there is a higher frequency of consanguinity, such as the Mennonites in Pennsylvania or the Amish, the frequency of MSUD is significantly higher at 1 newborn out of 176 live births. In Austria, 1 newborn out of 250,000 live births inherits MSUD. It also is believed to have a higher prevalence in certain populations due in part to the founder effect since MSUD has a much higher prevalence in children of Amish, Mennonite, and Jewish descent. [16-18]

Research directions

1. **Gene therapy:**

The gene therapy involves a healthy copy of the gene causing MSUD is produced and inserted into a viral vector. The adeno-associated virus vector is delivered one-time to the patient intravenously. Hepatocytes will take up vector and functional copies of the affected gene are MSUD patients will be expressed. This will allow BCAA to be broken down properly and prevent toxic build up. [19]

2. **Phenyl butyrate therapy:**

Sodium phenyl acetate/benzoate or sodium phenyl butyrate has been shown to reduce BCAA in a clinical trial done February 2011. Phenyl butyrate treatment reduced the blood concentration of BCAA and their corresponding BCKA in certain groups of MSUD patients and may be a possible adjunctive treatment. [20,21]

CONCLUSION:

Maple syrup urine disease (MSUD) is an uncommon, inherited inborn error of metabolism caused by defects in the branched-chain α-keto acid dehydrogenase complex metabolic disorder. The babies suffering from MSUD often had early appeared non-specific symptoms with poor feeding and lethargy, most cases later showed an odor resembling maple syrup and neurologic signs. For patients who were suspected of having MSUD, blood and urine concentrations of BCAA should be tested as soon as possible for early diagnosis. Specific MRI edema signal from brain suggests the possibility of MSUD. We should remember early intervention and treatment after diagnosis, with compliance of parents, would improve the patient's outcome. Classical MSD can be managed to allow a benign neonatal course, normal growth and development, and low hospitalization rates. However, neurologic function may collapse rapidly because of metabolic intoxication stimulated by common infections and injuries. Effective management of this biochemical disorder requires integrated management of general medical care and nutrition, as well as control of several variables that influence endogenous protein anabolism and catabolism, plasma amino acid concentrations, and serum osmolarity.

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