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Maple Syrup Urine Disease : A Rare Inherted Disorder of Amino Acid Metabolism

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ABSTRACT

Maple syrup urine disease is a rare and serious condition in which the amino acid metabolism is impaired. Mostly it is inherited in an autosomal recessive pattern in neonates from birth itself. Normally our body breakdowns proteins into amino acid and further amino acids are broken down and removed from our body, but in this disease body loses it's ability to breakdown amino acids causing harmful buildup of substances in blood and urine. It can cause life threatening cerebral oedema and dysmyelination in affected individuals. It is generally caused by the deficiency of enzyme complex (Branched chain alpha keto acid dehydrogenase(BCKDHA)) .this particular enzyme complex is necessary to breakdown the three branched chain amino acids(BCCA) leucine, isoleucine and valine, this results in the accumulation of all three amino acids in body producing toxic effects. The common symptoms of this disease in neonates includes: anorexia, sweet smell in the urine, irritability, weight loss. In classic MSUD neonates are even born asymptomatic but delay in treatment may lead to worsening of symptoms in their later stage of life. The toxic effects are due to accumulation of branched chain ketoacids(BCKAs)causing severe ketoacidosis and harmful effects of leucine on brain. However, this disease can be managed by a restricted diet containing low protein so that the three BCCAs are controlled to some extent and through continuous metabolic monitoring. Newborn screening for MSUD is also very common now a days for diagnosis of MSUD in newborns.

KEYWORDS

MSUD : maple syrup urine disease; BCKDHA : branched chain keto acid dehydrogenase E1 subunit alpha; BCCA : branched-chain amino acids; BCKA : branched-chain alpha-keto acid dehydrogenase; BCKAD : branched-chain α-ketoacid dehydrogenase.

INTRODUCTION

Individuals with multiple system dysfunction (MSUD) lack the necessary enzymes to break down three specific amino acids: valine, isoleucine, and leucine. They may also have insufficient amounts of these enzymes. These three amino acids accumulate in the bodies of MSUD patients, become poisonous to the body, and result in serious health problems since they are unable to be broken down by the body.

It is a metabolic abnormality brought on by branched-chain alpha-ketoacid dehydrogenase (BCKAD) complex activity. Branching-chain amino acid degradation is brought on by this complex:

Leucine
Isoleucine
Valine

Due to the disruption of branched-chain amino acid metabolism caused by the underlying deficiency in the BCKAD complex, there is an accumulation of branched-chain amino acids (BCAAs) in the plasma and corresponding branched-chain ketoacids in the urine.[11]

An inborn error of metabolism, maple syrup urine disease (MSUD) is brought on by defects in the branched-chain α-ketoacid dehydrogenase complex. This leads to elevated levels of α-ketoacids in urine, branched-chain amino acids (BCAAs) in plasma, and the production of alloisoleucine, the pathognomonic disease marker.[5]

Reduced activity of the branched-chain α-ketoacid dehydrogenase complex (BCKDC), which catalyzes the irreversible catabolism of branched-chain amino acids (BCAAs), results in maple syrup urine disease (MSUD), an autosomal recessive condition.[3]

EC 1.2.4.4 activity is necessary for the breakdown of branched-chain α-ketoacids, ketoisocaproate, ketomethylvalarate, and ketoisovalarate. These are the results of transamination of branched-chain amino acids leucine, isoleucine, and valine, respectively.In [4]

Neural and developmental delays, encephalopathy, eating issues, and a urine odor resembling maple syrup are the hallmarks of MSUD. Pathogenic homozygous or compound heterozygous mutations in BCKDHA, BCKDHB, DBT, or DLD, the catalytic subunits that make up BCKAD, may be the reason.[5]

The four components of the multimeric enzyme complex known as BCKD are the dihydrolipoyl transacylase (E2) subunit, the dihydrolipoamide dehydrogenase (E3) subunit, and the alpha and beta subunits of branched-chain keto acid decarboxylase (E1α and E1β). The cause of MSUD is mutations in the BCKDHA, BCKDHB, or DBT genes, which code for the E1α, E1β, and E2 subunits, respectively. These mutations account for 45, 35, and 20% of MSUD patients.[6]

When BCKDH is not functioning, the neurotoxic alpha-keto intermediates of the BCAAs leucine, isoleucine, and valine can build up in the blood and tissues and cause branched-chain ketoaciduria. The name of this condition comes from the peculiar sweet smell in the urine of affected patients. In the early neonatal stage, the majority of MSUD cases manifest in the typical form. Neurological dysfunction and catastrophic brain edema, which can be fatal, are the hallmarks of classic MSUD patients, who have little to no enzyme activity (0–2% of normal). Only a lesser percentage of patients with moderate MSUD (in which 3–30% of BCKDH activity is preserved) show less severe symptoms like as seizures, neurological damage, delayed development, failure to thrive, and ketoacidosis.Additionally, there is an intermittent variant of MSUD, in which patients have normal BCAA levels when asymptomatic but comparable BCKDH activity levels to those in intermediate MSUD (5–20% of normal). These people exhibit symptoms of MSUD when they are under stress or suffering from disease.[7]

MSUD can be classified into three or even four types: the classic type, the intermediate type, the intermittent type, and potentially the thiamine-responsive form. The varying severity and starting age of MSUD subtypes are explained by the varying levels of residual enzyme activity in each subtype. An genetic deficit in the activity of branched-chain 2-keto acid dehydrogenase (BCKD) is the cause of maple syrup urine disease. The three branched-chain amino acids (BCAAs), leucine, valine, and isoleucine, are thereby prevented from degrading at the 2-keto acid stage. Due to the reversibility of transamination, this causes an accumulation of branched-chain 2-keto acids as well as BCAAs in bodily fluids and tissues. The nonprotein branched-chain amino acid L-alloisoleucine, which is pathognomonic for MSUD, is formed endogenously as a result of defective isoleucine metabolism.[8] The main neurotoxic chemicals in MSUD that cause both acute and chronic brain damage are leucine and/or its

transamination product, 2-ketoisocaproate (KIC) [8]. It is believed that certain substances, particularly leucine and its transamination product 2-ketoisocaproic acid (KICA), which are consistently found in the plasma of MSUD patients at equimolar amounts, may have neurotoxic effects that could result in both acute and chronic brain dysfunction [1]. It is proposed that the accumulating KICA is the true cause of acute impairments in brain function based on in vitro research.[13]
With incredibly low residual BCKD activity (0–2%) in fibroblasts, approximately 80% of MSUD patients have the severe classic type.The majority of these subjects experience a severe encephalopathic crisis within their second week of life, culminating in a deep coma. With residual BCKD activity ranging from 3% to 40%, the remaining individuals have milder variant types. Generally, these variations are classified as intermediate, intermittent, or thiamine-responsive MSUD based on the clinical presentation and the biochemical response to thiamine treatment.(8).About 20% of MSUD patients have milder variant forms with later start or no brain symptoms, while the remaining 80% have a severe typical type with neonatal onset of severe encephalopathy and coma.[13]MSUD affects around one out of every 150,000 babies in outbred communities [2, 3], however it is more common in some endogamous groups [4,5]. Due to a founder form of BCKDHA that has drifted to a high carrier frequency (~10%) in some existing demes, severe (or "classic") MSUD affects as many as 1 in 400 births among Old Order Mennonites in North America.[10] The five clinical subtypes of MSUD have been identified based on severity: "Intermediate," "intermittent," "thiamine-responsive," "E3-deficient with lactic acidosis," and a "classic" neonatal severe type are among the variations.[12] Enzyme complex catalytic components include a decarboxylase (E1) consisting of two E1α and two E1β subunits, a transacylase (E2) core of 24 identical lipoate-bearing subunits, and a homodimer of a dehydrogenase (E3)[6]. The complex's subunits are produced in the “cytosol”, transported into the “mitochondria” where assembly takes place, and encoded by four nuclear genes [6]. An MSUD phenotype is caused by mutations in the genes encoding the E1α, E1β, and E2 subunits, whereas a more complex phenotype with lactic acidosis is caused by mutations in the E3 subunit [12].MSUD comes in four primary forms: 1. Classic: The most severe kind of maple syrup urine sickness is called classic MSUD. It's also the most typical. Typically, the first three days after birth are when symptoms appear. 2. Intermediate: Compared to traditional MSUD, this form is less severe. Children between the ages of five months and seven years old usually exhibit symptoms. 3. Intermittent: Children with intermittent MSUD develop normally up until symptoms are brought on by an infection or a stressful time. Compared to those with classic MSUD, those with intermittent MSUD can typically tolerate larger doses of the three amino acids. 4. Thiamine-responsive: Treatment for this kind of MSUD involves a restricted diet and high dosages of vitamin B1 (thiamine). Those with thiamine-responsive MSUD who receive treatment show increased tolerance to the three amino acids. [14]

Table 1 :Types of MSUD

TYPE	AGE OF ONSET	% WITH NORMAL BCKDH ACTIVITY
Classic	Neonatal	0%-2%
Intermediate	Variable	3%-30%
Intermittent	Variable	5%-20%
Thiamine responsive	Variable	2%-40%

ETIOLOGY

A malfunctioning branched chain a-ketoacid dehydrogenase (BCKD) complex is the cause of the incapacity to catabolize the BCAA. Branching-chain amino acids (BCKA) are created when the BCAA is transmitted, and BCKD oxidatively decarboxylates them. Nuclear genes encode all of the components of this mitochondrial multienzyme complex. According to Gillim et al. (1983) and Wagenmakers et al. (1984), two protein products are employed to control the activity-state of BCKD in various tissues, whereas four protein products provide stimulant action. Since that all cells have BCKD, this control is required to stop the depletion of BCAA. It is unclear why BCKD needs to be distributed throughout so many tissues. Out of four three genes that provide stimulant activity encode proteins that are unique to the substrates of BCKA. According to Yeaman (1989), the "fourth catalytic gene product collaborates with other mitochondrial complexes. While MSUD inheritance follows a straightforward autosomal recessive pattern, MSUD has been demonstrated to be caused by mutations in each of these three BCKD-specific genes" [1]. With a prevalence of one in 185,000 live births, this autosomal recessive disorder is brought on by a malfunction in the branched-chain 2-keto acid dehydrogenase (BCKD) enzyme, which results in an accumulation of the branched-chain amino acids (BCAA) valine, leucine, and isoleucine as well as their corresponding 2-ketoacids (BCKA) in bodily fluids and tissues [1,2]. The four components of the multimeric enzyme complex known as BCKD are the dihydrolipoyl transacylase (E2) subunit, the dihydrolipoamide dehydrogenase (E3) subunit, and the alpha and beta subunits of branched-chain keto acid decarboxylase (E1α and E1β).

Mutations in BCKDHA, BCKDHB, or DBT genes, which encode E1α, E1β, and E2 subunits, are the etiology of MSUD and affect 45, 35, and 20% of patients, respectively2. Leucine and 2-ketoisocaproic acid (KIC), a ketoacid generated from leucine, accumulate in MSUD, which is linked to neurotoxicity [2]. Branching-chain aminotransferase (BCAT), which is found in the mitochondria, converts leucine, isoleucine, and valine into the equivalent branched-chain α ketoacids (BCKAs) as the first step in the catabolism of BCAAs [3]. The second step of BCAA catabolism is the mitochondrial branched-chain α-ketoacid dehydrogenase complex (BCKDC) oxidatively decarboxylation of BCKAs, as shown by Reed et al. [4]. This is an irreversible step that occurs thermodynamically. The three catalytic components that make up BCKDC are as follows: dihydrolipoyl acyltransferase (E2), which is encoded by the DBT gene; dihydrolipoamide dehydrogenase (E3), which is encoded by the DLD gene; and branch-chain α-ketoacid decarboxylase (E1), which exists as an alpha2/beta2 heterotetramer and is encoded by the BCKDHA and BCKDHB genes, respectively [5]. Both covalent and allosteric mechanisms control BCKDC activity. It can be covalently controlled by two regulatory enzymes, BCKDC phosphatase (BCKDP) and BCKDC kinase (BCKDK), and allosterically inhibited by NADH and the CoA esters resulting from the oxidative decarboxylation of BCKAs [6]. By phosphorylating the E1α subunit of the BCKDH protein at codon Ser292, the former inhibits it, whereas the latter (BCKDP) activates it when it dephosphorylates the sameresidue[2]

The chromosome locations 19q13.1–13.2, 6q14, 1p31, 7q31–32, 16p11.2, and 4q22.1, respectively, have been assigned to the genes encoding the different catalytic subunits/components (E1α, E1β, E2, E3, kinase, and phosphatase). Maple syrup urine disease (MSUD) or branched-chain ketoaciduria (OMIM: 248600) is a metabolic failure in the oxidative decarboxylation of BCAAs caused by mutations in any of the BCKDC components (BCKDHA, BCKDHB, DLD, or DBT genes) [4,7]. Alloisoleucine, the pathognomonic marker of the disease, is elevated in plasma along with BCAAs and α-ketoacids and urine. [3] In newborn screening tests for the corresponding condition are crucial, as evidenced by the

presence of maple syrup metabolic problem in the Azerbaijani population, as determined by molecular genetic and biochemical approaches. On p. N400S 1199 A (Adenine) - G (Guanine), a homozygous substitution of adenine by guanine mutation has been discovered in the DBT (dihydrolipoamide branched-chain transacylase) gene. The genes encoding the alpha polypeptide of branched-chain keto acid dehydrogenase E1, BCKDHA, and beta polypeptide of BCKDHB, were found to be free of mutations.The discovered mutation, 1199 A (adenine)-G (guanine), is novel and hasn't been documented in any previous research. This mutation causes maple syrup illness by interfering with the metabolism of the amino acids valine, leucine, and isoleucine. Urine and plasma were tested for the amino acid content of valine, leucine, and isoleucine in order to diagnose maple syrup metabolic disease; a comparison of the data showed that the plasma analysis provided more useful information. [4]

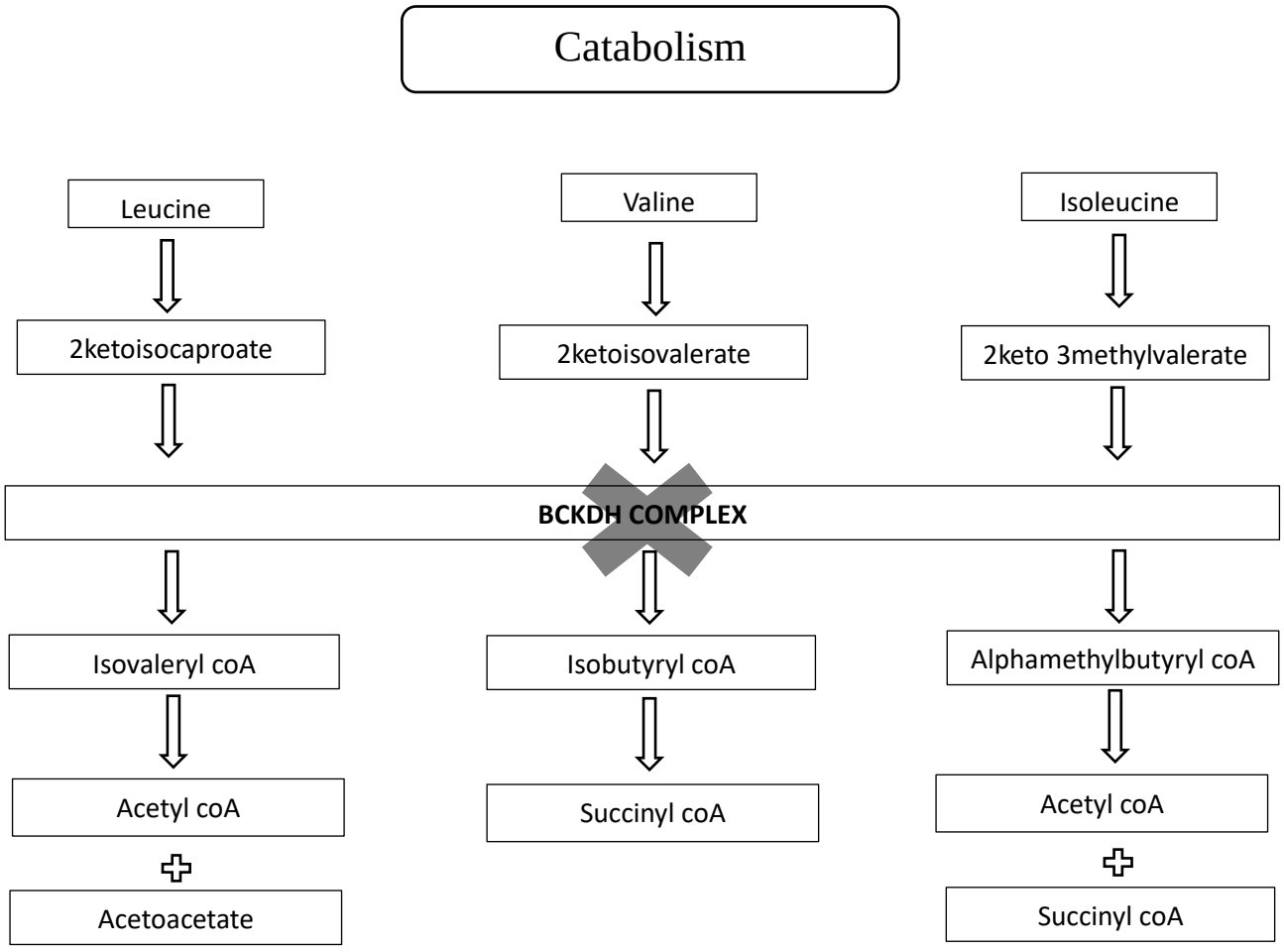

Figure 1 : Catabolism

EPIDEMIOLOGY

Maple syrup urine illness affects both males and females equally. It has an estimated worldwide frequency of one case per 185,000 live births. Higher incidences have been observed in populations with a higher level of consanguinity. The incidence among Ashkenazi Jews is believed to be one in every 26,000 live births. Maple syrup urine illness affects one out of every 380 infants among Mennonites. This is commonly referred to as a founder's effect in the BCKDHA (E1a) gene (c.1312T>A). In

Portuguese gypsies, 1.4% of cases result from a homozygous deletion (117delC) of the BCKDHA gene. It is expected that one instance occurs for every 71 births.[31]

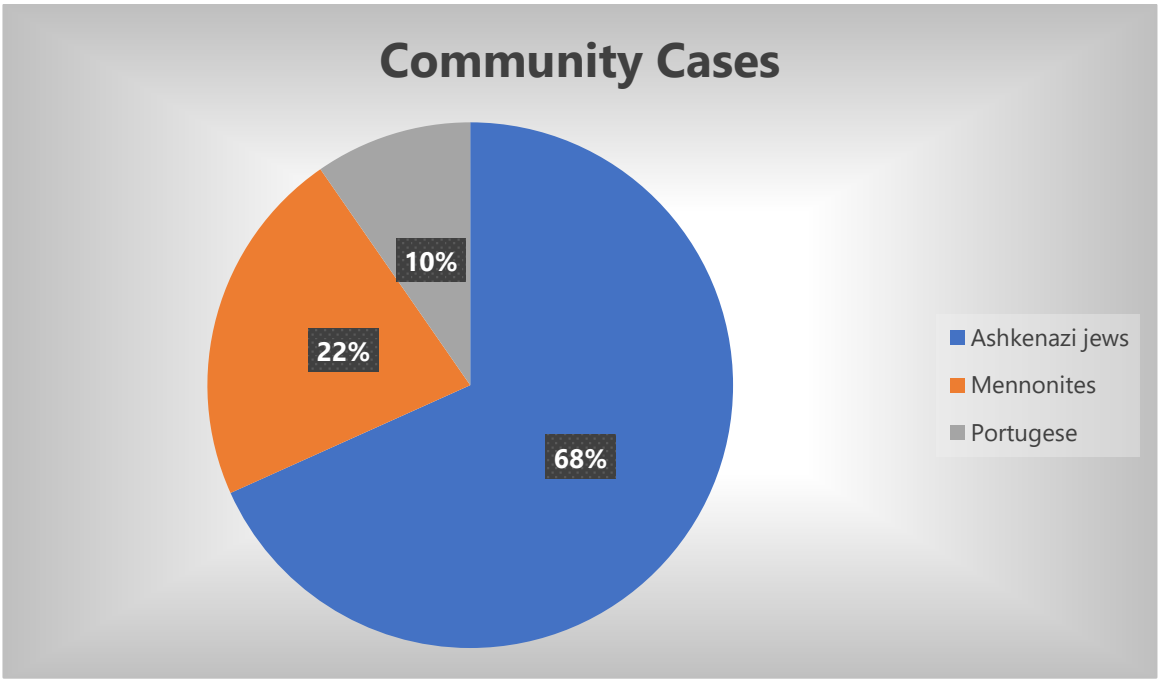

Figure 2 : Community cases

CLINICAL CHARACTERISTICS

Maple syrup urine disease (MSUD) is classified into three categories: classic (severe), intermediate, and intermittent in nature. While they are asymptomatic at birth, newborns with classic MSUD have a predictable course (12–24 hours) if they are not treated. The odour of maple syrup can be detected in cerumen, and blood contains elevated quantities of branched-chain amino acids (BCAAs)" leucine", "isoleucine", and "valine" and "alloisoleucine" along with a broad disruption of amino acid concentration ratios; Between two and three days. "Branched-chain alpha-ketoacids, acetoacetate, and beta-hydroxybutyrate" are found in urine after four to seven days of the onset of nonspecific early indications of metabolic intoxication, such as irritability, hypersomnolence, and anorexia. As the pleasant maple syrup stench appears in the urine, worsening encephalopathy presents seven to ten days later with lethargy, apnea, opisthotonos, and reflexive "fencing" or "bicycling" movements. A coma, central respiratory failure, and serious cerebral edema are the end results of severe intoxication. When enough catabolic stress is applied, people with intermediate MSUD can develop severe metabolic intoxication and encephalopathy. These people have partial "branched-chain alpha-ketoacid dehydrogenase deficiency", which only sometimes manifests or responds to dietary thiamine therapy. In the era of newborn screening (NBS), the majority of people who would have experienced neonatal signs of MSUD continue to be asymptomatic with continuous treatment compliance because asymptomatic infants identified by NBS are promptly treated.[1] The earliest weeks of infancy are typically marked by acute episodes of encephalopathy in affected patients, which are linked with seizures, coma, and potentially fatal cerebral edema. Progressive neurological decline with motor delay, ataxia, intellectual incapacity, and psychiatric disorders then ensues.[2] The classic presentation is characterized by a delayed developmental period, feeding difficulties, failure to thrive, and a maple syrup odour in the urine

and cerumen. If untreated, this can result in irreversible neurological complications such as metabolic decompensation, stereotypical movements, and even death.[5] During periods of metabolic decompensation, patients with the classic form typically experience acute episodes of severe vomiting, hypotonia, and encephalopathy. These symptoms are linked to seizures, coma, and potentially fatal brain edema. Additionally, there is a significant rise in the concentrations of BCAA and BCKA, particularly leucine and α-KIC.[9] Traditional MSUD is one of the most unstable and hazardous hereditary metabolic disorders: prolonged amino acid and neurotransmitter imbalances increase the risk of mental disorders, intellectual disability, and executive dysfunction; acute elevations of leucine and α-ketoisocaproic acid (αKIC) cause metabolic encephalopathy and critical brain edema.[10]

TREATMENTS

Mostly liver transplant is used for the treatment of MSUD. Along with it we use Sodium Phenylbutyrate (NaPBA) therapy, Parentral amino acid mixture therapy, Gene therapy, Metformin and some other therapies.

LIVER TRANSPLANT

In MSUD patients, liver transplantation (LT) can partially restore enzymatic activity, as the liver is responsible for around 15% of enzymatic BCKDH synthesis. Using deceased donors, it has been discovered that individuals with MSUD have a reduction in leucine content several hours following LT. Domino liver transplantation (DLT) uses the structurally normal livers of MSUD patients as a source of liver grafts.[16] According to the effectiveness of LT for MSUD, maintaining peripheral amino acid homeostasis only requires injecting roughly 10% of normal BCKDH activity on a whole body basis. Normal plasma leucine levels are achieved when more than 90% of BCAAs are broken down by the receiver with MSUD's transplanted liver.[17] With regard to the optimization of both physical and neurological development, LT not only reduces high and fluctuating BCAA levels but also shields kids from necessary amino acid shortages. It proved successful to use a related donor in Liver Transplant for MSUD, and the MSUD patient's liver was successfully used in a domino transplant. The choice to utilize a related donor in this instance was made in light of the donor's clinical profile as well as the evidence of normal BCAA levels. Because the test is not generally accessible and, more significantly, because the disease is linked to both allelic and locus heterogeneity, routine donor genotyping may not be possible. Expanding the use of related donors in MSUD will require more research with this patient population.[16]

ROLE OF SODIUM PHENYLBUTYRATE (NAPBA)

Sodium phenylbutyrate effectively scavenges nitrogen. It is mostly used to treat problems related to the urea cycle. Also, NaPBA can lower, levels of branched-chain amino acids. Patients with intermediate MSUD can use this therapy.[19]During an acute decompensation, BCAA and ketoacids can also be fastly corrected using hemodialysis and peritoneal dialysis. [18]

PARENTRAL AMINO ACID MIXTURE

A deficit in branched-chain keto-acid dehydrogenase is the cause of classic maple syrup urine disease (MSUD). The branched-chain amino acids (BCAA) leucine (Leu), valine, and isoleucine as well as 2-keto acids are significantly elevated in plasma, urine, and cerebrospinal fluid as a result of the enzyme

deficiency. Amino acid chromatography is a diagnostic tool for MSUD. Restricting the amount of dietary BCAA to what can be directly absorbed into body protein is part of the long-term therapy plan for patients with MSUD. In addition to providing normal to high levels of nonbranched-chain amino acids—which are made possible by synthetic BCAA-free amino acid mixtures—this tightly restricted diet also provides sufficient energy and other nutrients to support protein synthesis. Early detection and management of circumstances that could result in protein catabolism helps to prevent acute intercurrent bouts of decompensation. Prolonged imbalances of circulating amino acids may have more subtle, long-lasting impacts on brain structure and function than acute metabolic decompensations, which can result in unexpected death from cerebral oedema and brain-stem compression (Ogier de Baulny H et al 2012). Therefore, acute episodes of metabolic decompensation in MSUD patients are considered life-threatening conditions. Dietary deviations, inadequate calorie or amino acid intake (anorexia, fasting), injuries, or infections can all cause them (Strauss et al 2010). Even in extreme circumstances, the nutritional guidelines for treating acute episodes are similar to those used in maintenance therapy: cut out Leu from the diet right once and encourage protein synthesis to quickly lower blood Leu concentrations. Combinations of amino acids free of branch chain amino acids (BCAAs) are necessary to help incorporate excess Leu into new proteins, which lowers its circulation concentration and prevents its harmful effects. BCAA-free amino acid combinations are often fed by nasogastric tube feeding together with lipids and carbohydrate polymers. Absorption of the BCAA-free amino acid mixture is troublesome in patients who present with stomach intolerance, and can only be achieved with a gradual, continuous nasogastric infusion. It is necessary to modify the isoleucine and valine supply in accordance with their plasma concentrations. Nevertheless, during gastroenteritis episodes, this therapy method typically fails, making therapeutic management challenging. Leu and harmful metabolites have been effectively removed using dialysis. Nonetheless, dangers and consequences, such as infection, are linked to extracorporeal dialysis procedures. Furthermore, not all centers have access to them, and they need specialized knowledge... When high plasma leucine concentrations exacerbate catabolic episodes, the question of whether to begin dialysis or pursue medicinal therapy must be answered. The decision is challenging since it is impossible to pinpoint which patients may experience life-threatening problems with their central nervous systems if dialysis is postponed. In order to get around these issues and prevent dialysis, we created and assessed a novel parenteral amino acid combination that doesn't contain BCAA. Here, we compare the safety and effectiveness of this novel treatment to that of conventional enteral feeding using nasogastric tube in MSUD patients experiencing metabolic decompensation. Specifically, we monitored the decline in plasma Leu concentration throughout the first three days of the acute episode, which is thought to be the most vulnerable time for problems with the central nervous system.[20]

GENETHERAPY

In an extremely rare autosomal recessive metabolic disorder known as maple syrup urine disease, the mitochondrial enzyme complex branched-chain 2-ketoacid dehydrogenase (BCKD), which is involved in the second step of branched-chain amino acid (BCAA) catabolism, malfunctions.[1-2] This condition is characterized by a massive increase in BCAA and associated branched-chain 2-ketoacids (BCKA) in tissues and biofluids.[3] An the formation of leucine and 2-ketoisocaproic acid is the cause of the neurotoxicity seen in MSUD. Mutations in branched-chain keto acid decarboxylase alpha and beta subunits [E1α and E1β] and dihydrolipoyl transacylase [E2] subunit (BCKDHA, BCKDHB, and DBT)

cause MSUD in 45%, 35%, and 20% of patients, respectively. The severe form of MSUD affects 85–95% of patients; in the event that treatment is not received, symptoms include cerebral edema, unconsciousness, and early death. Less than 3% of these patients still have BCKD activity.[4] Given its association with a reduced quality of life and inability to mitigate long-term neuropsychiatric effects, the long-term management of MSUD—which hinges on a strict and permanent dietary restriction of BCAAs in conjunction with an oral amino acid-free medication—represents an unmet need.[4-6] Orthotopic liver transplantation (OLT) is an effective treatment for MSUD, despite some risks. It stabilizes neurocognitive deficits, avoids acute decompensation, maintains clinical and metabolic stability, and allows dietary restrictions to be lifted.[7-9] Because of its well-established pathophysiology, highly instructive biochemical readouts, and the evidence provided by OLT that, even in cases where the enzyme is widely expressed, restoring only liver BCKD activity—which accounts for 9%–13% of total body BCKD activity—is therapeutic, MSUD, like many other autosomal recessive monogenic disorders of metabolism, is a good candidate for gene therapy.[10] Genes can be transferred to the liver or other organs with the help of adeno-associated virus (AAV) vectors.[11] In addition, they have been used in human clinical trials (such as for ornithine transcarbamylase deficiency) to treat inborn metabolic errors in animal models of urea cycle disorders, organic acidemia, phenylketonuria, and other conditions.[17,18,19] There have been two recent reports of proof-of-concept studies regarding the efficacy of AAV gene therapy in mice with MSUD.[20,21] We evaluated two vectors that carried the human BCKDHA gene under the control of either a liver-specific hAAT promoter or a ubiquitous EF1α. These vectors were encapsulated in AAV capsids of serotype 8, which primarily targets the liver but also other organs (like the heart). The mice were injected with the vectors at birth in a BCKDHA−/− model, which replicates the severe human MSUD phenotype. It was demonstrated that although the AAV8-hAAT-hBCKDHA vector exhibited a more limited effectiveness, intravenous neonatal gene therapy employing the AAV8-EF1α-hBCKDHA vector resulted in long-lasting disease recovery.[20] In a hypomorphic mouse model for the Dbt gene with a milder phenotype, DBT gene therapy—powered by the ubiquitous CB7 promoter encapsidated in muscle-tropic AAV9 capsids—was demonstrated to provide significant disease rescue following intramuscular or intravenous injection in young adult mice. In contrast, liver-specific and muscle-specific strategies achieved more limited efficacy. As far as we are aware, no mouse model for Bckdhb has been published.[21]

GROWTH HORMONE

A genetic metabolic condition of amino acid metabolism known as Maple Syrup Urine Disease is brought on by a deficit in the enzyme branched chain ketoacid dehydrogenase, which causes branched chain amino acids (BCAA) including valine, isoleucine, and leucine to accumulate. The accumulation of these acids causes encephalopathy, cerebral edema, and progressive metabolic ketoacidosis if left untreated. The disease is generally identified by the metabolic newborn screen and is managed by restricting the amount of natural protein that contains branched chain amino acids in the diet while supplying sufficient vital non-branched chain amino acids with special medical foods [1]. Decreased natural protein tolerance brought on by physiological stress or catabolic conditions that release branched chain amino acids from skeletal muscles can also cause metabolic crises. Acute sickness can cause brain damage, cerebral edema, and metabolic crises in people with MSUD. Even though MSUD has been recognized for many years, it is a rare condition, and management guidelines have only recently been released. [2,3]. This report describes a situation when the methods outlined in these guidelines failed to

control a child's metabolic crisis. We present the use of growth hormone as an adjuvant therapy, which is corroborated by recent research in pediatric burn patients [9] and is mentioned in earlier literature for MSUD [4], as well as in several recent case series in other hereditary metabolic illnesses [5-8]. The 2014 Maple Syrup Urine Disease Nutritional Management Guidelines and the 2013 Genetic Metabolic Dietitians International guidelines offer suggestions for the treatment of patients experiencing a metabolic crisis. Built around strict dietary control to enhance anabolism, which includes providing up to 150% of the average energy intake, BCAA-free protein for one to two days, and electrolyte and valine supplements. In addition to these nutritional management strategies, seriously ill patients may need insulin infusion, dialysis, hemofiltration, parenteral nutrition and/or tube feeding while the source of the decompensation is addressed [2,3]. During times of metabolic stress, “protein anabolic” pharmacotherapy may be used to supplement dietary control and, ideally, lessen the need for dialysis and other invasive procedures. The data on “protein anabolic” medication in this population is scarce due to the rarity of hereditary metabolic disorder [4,10]. On the other hand, numerous excellent research on protein anabolic medication in that population have been conducted, and the well-documented “protein catabolic” state of children who have severe burns has been addressed. [9] In this research, it is suggested that the literature offers an important source of information that might be used in the treatment of children who have genetic metabolic diseases.[22]

METFORMIN

Our previous study demonstrated that metformin improves metabolic equilibrium and inhibits BCAA-derived ketoacidosis in fibroblast cells isolated from MSUD patients.[14] To figure out if metformin increases longevity and/or delays pathology in iMSUD mice, we used the previously described method of feeding.[15] A malfunction in the enzyme BCKDH results in Maple Syrup Urine Disease (MSUD), a genetic condition. This leads to an accumulation of branched-chain amino acids (BCAA) and branched-chain ketoacids (BCKA) in bodily fluids (e.g., keto-isocaproic acid from the BCAA leucine). Patients experience a range of clinical symptoms as a result, including a less well-known dysfunction of the skeletal muscles. At doses relevant to the disease, KIC suppresses mitochondrial activity. Reduced muscle fiber diameter indicates significant skeletal muscle dysfunction in a mouse model of intermediate MSUD (iMSUD). Since MSUD is an rare disease, novel pharmacological strategies are needed. We showed that metformin, a popular anti-diabetic medication, reduces KIC levels in patient-derived fibroblasts by 20–50% using a 96-well plate (liquid chromatography–mass spectrometry) based drug-screening apparatus. Metformin treatment restored levels of mitochondrial metabolites and significantly reduced KIC levels in muscle (by 69%) and serum (by 56%) extracted from iMSUD mice. The drug also reduced the expression of BCAT, the mitochondrial branched chain amino transferase that produces KIC in skeletal muscle. This demonstrates that by decreasing mitochondrial KIC synthesis, metformin can enhance skeletal muscle homeostasis in MSUD.[28]

REACHING THE RECOMMENDED BLOOD CONCENTRATIONS OF BCAA

For those with multiple sclerosis (MSUD), dietary BCAA restriction tries to prevent and treat BCAA deficits while achieving and maintaining plasma BCAA concentrations as near to normal. Finding the plasma amounts that have negative effects has been the main focus of studies examining BCAA concentrations in MSUD. There are differences in the effects of elevated LEU concentrations on social and psychomotor function, but they are generally linked to abnormal brain morphology and cognitive

impairment. Skin, eyes, and digestive tract epithelial damage is severe but reversible when low plasma BCAA levels, particularly ILE and to a lesser extent VAL, are present. Poor growth has been associated with a deficiency of BCAAs. While easing the dietary restriction on BCAAs in adults and adolescents has been noted in research and suggested to enhance quality of life.[29] There is a chance that this practice won't work out well, and it hasn't been thoroughly or impartially assessed. Modern dietetic practices After receiving SLC7A5 substrate-enriched formulas as a prospective treatment from birth, 21 (51%) of the 41 BCKDHA c.1312 T > A the homozygotes (DOB 2005-2018) were identified for the umbilical cord molecular testing based on their parental carrier status. The majority of these individuals were diagnosed at an average of 12 hours of life and remained asymptomatic during a safe perinatal transition at home. Through state newborn screening, twenty babies (or 49%) were found. Three newborns in the latter group were hospitalized between the ages of seven and eleven due to metabolic encephalopathy; the newborns in this category received diagnosis at an average of five days and in some cases showed symptoms involving elevated plasma leucine amount (1123–2769 μmol/L). If a child exhibited no or minimal signs of encephalopathy, could handle a substantial amount of "sick-day" formula, and had parents willing to devote themselves to strict clinical and amino acid monitoring in an outpatient setting, the remaining 17 (85%) babies diagnosed by newborn examination received effective therapy at home.[30]

OTHER THERAPY

MEDICAL NUTRITIONAL THERAPY

Clinical validation and a favorable outcome from the neonatal screening are necessary before nutritional therapy can begin. Dietary restriction of branched-chain amino acids continues to be the cornerstone of therapy.[25] These actually will….. Boost your anabolism, Stop the catabolic process, Encourage balanced development and weight gain, Maintain Cognitive Ability, Toxic metabolites can be decreased by allowing the restriction of branched-chain amino acids in the diet, Sustain the necessary treatment ranges for plasma BCAA levels, Check for thiamine sensitivity.[24]

HOME THERAPY

In order to identify elevated urine branched-chain ketoacids, providers may be advised to utilize a dinitrophenylhydrazine reagent. This makes it possible to identify and treat mild to severe cases of acute metabolic decompensation at home in a timely manner.[26][24]

TREATMENT OF ACUTE DECOMPOSITION

The most common causes of metabolic decompensations (plasma leucine >380 micromol/L) are infections and non-compliance with diet. Dietary noncompliance increases the levels of BCAAs and infrequently leads to encephalopathy and decompensation. Suppressing protein catabolism and promoting protein synthesis is the primary goal of treatment.[27] In more serious situations, management techniques include: addressing the underlying stressor that is generating the metabolic crisis successfully Limit your protein intake for a full day or two.Give a sufficient amount of calories Drink enough water to keep your metabolism in balance. Provide cofactors as a supplemental resource. Get rid of harmful metabolites Address any related clinical aftereffects Address anomalies in metabolism[24]

IN HOSPITAL THERAPY

Effectively managing the underlying stressor (e.g., fever, dehydration, infection, and inflammation) is one of the objectives and therapeutic approaches of in-hospital therapy. -Antiemetic medications like ondansetron are recommended to treat nausea and vomiting.[24] a decrease in leucine levels of at least 750 micromol/L every 24 hours. Insulin and glucose infusions can be used to reduce leucine levels. Leucine levels should ideally be kept between 200 and 300 micromol/L. Total parenteral nutrition can be used to return 25–50% of the normal consumption of protein into the diet after clinical recovery. Over the next few days, this intake may be increased in accordance with the clinical circumstances. At least 1.25 times the weight or surface area must be supplied in EER. Between 40% to 50% of total calories should come from fat. Parenteral and enteral feeding can be used in tandem to meet nutritional objectives.

One should supplement with 20–120 mg/kg/day of isoleucine and valine, respectively. Supplemental intake is modified to keep plasma concentrations between 400 and 600 micromol/L constant. Tyrosine supplementation by enteral (100–400 mg/kg/day) for the treatment of localized or widespread dystonias.

Supplementing with 150–400 mg/kg of glutamine and alanine per day each. Add more amino acids without BCAAs. Keep sodium levels within the normal range for your body. Address underlying imbalances between acid and base. Maintain urine production and steer clear of osmolarity swings greater than 5 mosm/L every day. Take care of hypophosphatemia and hypokalemia that are brought on by IV glucose and insulin treatment.[26][24]

DISCUSSION

The prevalence of MSUD worldwide is roughly 1 in 85,000. Most clinics see very few patients with MSUD, despite the fact that there are communities with much higher prevalence, such as the old-order Mennonite community, where the incidence can reach one in every 200 births. Collecting outcomes information without multicenter collaboration is impossible with such small patient populations. Case studies and series make up the majority of articles; these are typically retrospective and don't include information from age-matched controls. Along with consensus findings from two Delphi surveys and one nominal group session, the MSUD Nutrition Management Guideline fills in these gaps in the peer-reviewed literature by providing a thorough analysis of gray literature. For many illnesses, there are already treatment suggestions as well as guidelines available; however, these often depend on expert opinion, consensus, or a review of the literature. Incorporating information gathered from all sources and giving the resulting suggestions systematic rating scores is the methodology used for this guideline project. Essentially, this guideline is based on five research questions. The selection process was based on the workgroup's evaluation of nutrition-related themes that were deemed to have distinct viewpoints or were underrepresented in the literature. The ratings assigned to the recommendations resulting from the assessment of all sources vary substantially. Studies that were either not published or very few, did not demonstrate statistical significance, or were primarily addressed by consensus were the reasons for the recommendations with the lowest scores. That being said, an advice with a low score does not necessarily mean it is invalid or should be disregarded. It highlights, nevertheless, the lack of credible peer-reviewed studies presenting thoughtfully planned studies on the topic. Novel and innovative treatments for MSUD are currently undergoing clinical trials. These include sodium phenylbutyrate, carnitine, hepatocyte transplantation and antioxidants. Too little research has been done to say how these

adjuvant medications would impact or change dietary guidelines. These treatments will be included in future iterations of the recommendations. The guidelines include recommendations for nutrition monitoring, age-appropriate nutrient intake, background information on MSUD, and links to appropriate data and resources for putting the recommendations into practice. They also include suggestions based on the research's questions. Mennonite children with MSUD received expensive, dispersed medical care up until 1989. These children suffered severe brain damage, and nearly half of them passed away from brain herniations. 79 MSUD children now call the Clinic for Special Children, which opened its doors in 1989, home. The focus of the Clinic's early research was on integrating metabolic care into standard pediatric therapy. This led to affordable on-location amino acid testing.

CONCLUSION

Maple syrup Urine disorders is a rare, serious metabolic disease that interferes with the metabolism of amino acids. Early discovery through birth screening and lifelong nutritional management are critical for MSUD patients' well-being, allowing them to live healthy lives while avoiding the condition's catastrophic neurological repercussions.

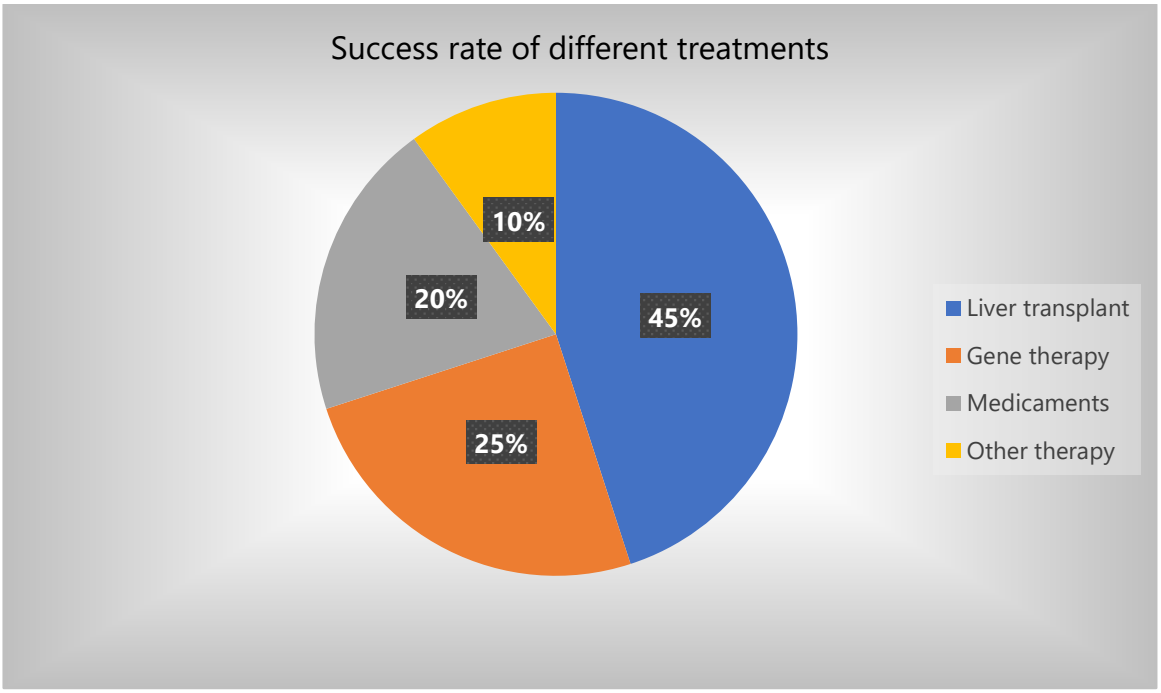

Figure 3 : Success rate of different treatments

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