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A COMPREHENSIVE REVIEW ON MAPLE SYRUP URINE DISEASE (MSUD)

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Abstract

Maple syrup urine disease (MSUD) is an autosomal recessive neurometabolic disorder caused by severe deficiency of branched-chain α-keto acid dehydrogenase complex activity, which catalyzes the oxidative decarboxylation of the branched-chain α-keto acids (BCKA). The metabolic blockage results in tissue accumulation and high urinary excretion of the branched-chain amino acids (BCAA) leucine, isoleucine and valine, as well as alloisoleucine, and their respective BCKA α-ketoisocaproic (α-KIC), α-ketoisovaleric and α-keto-β- methylvaleric acids. Affected patients usually manifest acute episodes of encephalopathy associated with seizures, coma and life-threatening cerebral edema in the first weeks of life, which is followed by progressive neurological deterioration with motor delay, ataxia, intellectual disability and psychiatric symptoms. variants that have no known association with genotype. 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 decompensation, and death if left untreated. Treatment consists of dietary restriction of BCAAs and close metabolic monitoring. Clinical outcomes are generally good in patients where treatment is initiated early. Finally, we will discuss recent evidence that implicates the relevance of BCAA metabolism in other neurological disorders. An understanding of the role of BCAAs in the central nervous system may facilitate future identification of novel therapeutic approaches in MSUD and a broad range of neurological disorders.

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder caused by defects in the branched chain α- ketoacid dehydrogenase complex (BCKDC), which impairs the breakdown of branched chain amino acids (BCAAs) leucine, isoleucine, and valine leading to their toxic deposition in plasma and tissues (Blackburn et al., 2017; Lyons et al., 1973). This accumulation disrupts brain metabolism and results in a spectrum of clinical and neurological manifestations. MSUD typically presents in the neonatal period with poor feeding, vomiting, lethargy, dystonia, and seizures, often progressing to encephalopathy and coma if untreated.

The disorder was first described in 1954 by Menkes and colleagues as a progressive neurodegenerative condition characterized by a

distinctive maple syrup like odor in the urine and cerumen, attributed to sotolone, a metabolite of isoleucine. MSUD is also known as branched chain ketoaciduria or BCKD deficiency. It serves as a classic model for understanding the neurotoxic effects of amino acid imbalances in inborn errors of metabolism.

Globally, MSUD has an estimated incidence of approximately 1 in 185,000 live births. However, significantly higher rates occur in certain founder populations due to specific genetic variants, such as 1 in 380 in Old Order Mennonites (primarily due to a common BCKDHA variant) and elevated incidence in Ashkenazi Jewish and some consanguineous populations. The disorder affects males and females equally.

The BCKDC is a mitochondrial multienzyme complex responsible for the oxidative decarboxylation of BCAAs after their transamination. Pathogenic variants in BCKDHA (E1α), BCKDHB (E1β), DBT (E2), or rarely DLD (E3) reduce or abolish enzyme activity. Leucine and its ketoacid (α-ketoisocaproic acid) are particularly neurotoxic. They compete with other large neutral amino acids for transport across the blood-brain barrier, leading to depleted neurotransmitters (e.g., glutamate, dopamine, serotonin), impaired energy metabolism (Krebs cycle disruption), oxidative stress, cerebral edema, and myelin abnormalities. Untreated classic MSUD can progress rapidly to coma and death within the first weeks of life.

Maple Syrup Urine Disease is considered one of the most clinically significant inborn errors of amino acid metabolism because of its potentially life threatening complications and long term neurological consequences. Early diagnosis and nutritional intervention are essential to prevent irreversible brain damage, developmental delay, and mortality. Increasing awareness regarding newborn screening programs has improved early detection of MSUD world-wide. However, limited healthcare resources and delayed diagnosis remain major challenges in developing countries. Thus understanding the pathophysiology, diagnosis, and nutritional management of MSUD is important for healthcare professionals.

Recent studies have showed significant advancements in the diagnosis and management of Maple Syrup Urine Disease. Developed newborn screening techniques using tandem mass spectrometry have enabled early identification of affected infants before the onset of severe symptoms. Research has also highlighted the neurotoxic effects of elevated leucine concentrations on brain metabolism and neurotransmitter function. Several other studies have emphasized the effectiveness of dietary management using branched-chain amino acid restricted diets and specialized medical formulas in reducing metabolic crises and improving growth outcomes.

Despite advancements in diagnosis and treatment, several challenges still exist in the management of Maple Syrup Urine Disease. Long term dietary compliance remains difficult for many patients due to strict protein restrictions and limited accessibility of specialized medical foods. Limited literature is available regarding the psychosocial impact, nutritional deficiencies, and quality of life among patients with MSUD. More research is therefore needed to develop affordable treatment strategies, improve nutritional management, and explore advanced therapies.

Aims and Objectives

- To provide a detailed overview of the genetic and biochemical mechanisms underlying maple syrup urine disease.
- To summarize the various clinical presentations and diagnostic methods for early and accurate identification of MSUD.
- To review recent advances and future therapeutic approaches for MSUD management.

Literature Review Pathophysiology

Maple syrup urine disease is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase (BCKD) enzyme complex, which catalyzes the decarboxylation of the alpha-keto acids of leucine, isoleucine, and valine to their respective branched-chain acyl-coenzyme As (acyl-CoAs). These are further metabolized to yield

acetyl-CoA, acetoacetate, and succinyl-CoA. The BCKD enzyme complex, which is associated with the inner mitochondrial membrane, has three different catalytic components (ie, E1, E2, E3) and two associated regulatory enzymes (ie, BCKD phosphatase, BCKD kinase). In addition, the E1 component consists of two distinct subunits (ie, E1 alpha, E1 beta), which form an alpha-2 beta-2 heterotetramer. The E3 component is associated with two additional alpha-keto acid dehydrogenase complexes, namely pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase.

Mutations in E1, E2, or E3 cause maple syrup urine disease. No clear genotype-phenotype correlation between molecular and clinical phenotypes is known, with the exception of mutations in E2, which cause thiamine-responsive maple syrup urine disease. Mutations in E3 cause additional deficiencies of pyruvate and alpha-ketoglutarate dehydrogenases. Mutations in the regulatory enzymes have not been reported.

Accumulation of plasma leucine causes neurologic symptoms. Leucine is rapidly transported across the blood-brain barrier and is metabolized to presumably yield glutamate and glutamine. The accumulation of plasma isoleucine is associated with the maple syrup urine odor.

Classification based on phenotype Classic maple syrup urine disease

Classic maple syrup urine disease is the most common type. In classic maple syrup urine disease, little or no BCKD enzyme activity (usually <2% of normal) is present. Infants show symptoms

within the first week of life. They generally have poor tolerance for the branched-chain amino acids (BCAAs), so dietary protein must be severely restricted.

Intermediate maple syrup urine disease

Intermediate maple syrup urine disease is a variant of classic maple syrup urine disease but is less common. Patients with intermediate maple syrup urine disease have a higher level of BCKD enzyme activity (approximately 3-8% of normal), and they can usually tolerate a greater amount of leucine.

Intermittent maple syrup urine disease

Intermittent maple syrup urine disease, the second most common type of maple syrup urine disease (after the classic type), is a milder form of the disease owing to the presence of greater enzyme activity (approximately 8-15% of normal).

Thiamine-responsive maple syrup urine disease

The descriptive term thiamine-responsive maple syrup urine disease reflects the treatment of this rare type of maple syrup urine disease. Giving large doses of thiamine to the thiamine-responsive child increases BCKD enzyme activity, leading to a breakdown of the BCAAs.

E3-deficient maple syrup urine disease

E3-deficient maple syrup urine disease (dihydrolipoamide dehydrogenase deficiency [DLDD]) is a very rare type of maple syrup urine disease. These patients have combined deficiencies of the BCKD enzyme complex and pyruvate and alpha-ketoglutarate dehydrogenases.

Diagnosis of Maple Syrup Urine Disease (MSUD)

Maple Syrup Urine Disease (MSUD) is an inherited metabolic disorder caused by deficiency of the branched-chain α-ketoacid dehydrogenase complex. This defect leads to accumulation of branched-chain amino acids, mainly leucine, isoleucine, and valine, in blood and tissues. Early diagnosis is important because delayed treatment can result in neurological damage and death.

Clinical Diagnosis

The diagnosis is initially suspected from clinical symptoms. Infants with classic MSUD usually appear normal at birth but develop symptoms within the first few days of life. Common manifestations include poor feeding, vomiting, lethargy, irritability, hypotonia, seizures, and developmental delay. A characteristic sweet odor similar to maple syrup or burnt sugar in urine is an important diagnostic clue.

Newborn Screening

Newborn screening is considered the most effective method for early detection of MSUD. Tandem mass spectrometry (MS/MS) is used to identify elevated concentrations of branched-chain amino acids, particularly leucine and isoleucine, in dried blood spots collected from newborns. Early screening helps prevent severe neurological complications through timely dietary management.

Plasma Amino Acid Analysis

Confirmation of MSUD is achieved by plasma amino acid analysis. Patients show markedly elevated levels of leucine, isoleucine, and valine. The presence of alloisoleucine is considered a specific biochemical marker for MSUD and helps differentiate it from other metabolic disorders.]

Urine Organic Acid Analysis

Urine examination reveals increased branched-chain ketoacids and ketones. Organic acid analysis is usually performed using gas chromatography–mass spectrometry (GC-MS). This test supports the diagnosis and helps assess the severity of metabolic imbalance.

Molecular Genetic Testing

Genetic testing is used to confirm mutations in genes responsible for the branched-chain α-ketoacid dehydrogenase complex, mainly BCKDHA, BCKDHB, and DBT. Molecular diagnosis is useful for carrier detection, genetic counseling, and prenatal diagnosis in affected families.

Enzyme Assay

Enzyme activity testing may also be performed in leukocytes or cultured fibroblasts to evaluate the activity of the branched-chain α-ketoacid dehydrogenase complex. Reduced enzyme activity confirms the diagnosis.

Recent Advances and Future Direction

Liver transplantation has emerged as a transformative therapy for classical MSUD, providing approximately 9–13% of normal whole-body BCKDH activity, which is sufficient to restore metabolic homeostasis, eliminate dietary restrictions, and prevent life-threatening decompensations. Recent cohorts report excellent graft and patient survival (often 100% in the short-to-medium term) and significant neurodevelopmental benefits when performed early, although pre-existing neurological injury is not reversed (Deon et al., 2023; Khalaf-Nazzal et al., 2026; Strauss et al., 2020).

Gene therapy has shown considerable promise in preclinical models. Neonatal liver-directed AAV8 gene therapy achieved sustained disease rescue in MSUD mouse models (Pontoizeau et al., 2022). More recent work using a dual-function recombinant AAV9 vector delivering codon-optimized BCKDHA and BCKDHB genes successfully prevented perinatal death, normalized growth, restored enzyme activity, and stabilized biomarkers in both mouse and calf models of MSUD. Treated animals progressed to an unrestricted diet, highlighting the potential of a one-time systemic gene replacement strategy as an alternative to lifelong dietary therapy and liver transplantation (Wang et al., 2025; Strauss group, 2025). Muscle-directed AAV approaches are also under investigation to address limitations of liver-only targeting.

Multi-omics studies (metabolomics, lipidomics, and proteomics) have further clarified persistent metabolic imbalances even after liver transplantation, including alterations in redox homeostasis, energy metabolism, sphingolipids, and oxidative stress pathways. These findings identify potential adjunct therapeutic targets beyond current approaches (2025 pilot study).

Conclusion

Maple Syrup Urine Disease is a rare but serious inherited metabolic disorder result in a from defective metabolism of branched-chain amino acids. Early diagnosis through newborn screening and nutritional intervention are critical for preventing neurological damage and mortality. Emerging treatment modalities such as liver transplantation and genetic research provide hope for improved long-term outcomes. Gene therapy and enzyme replacement are under investigation. Advances in molecular genetics have improved

genotype-phenotype correlations, aiding personalized management. Gene therapy and enzyme replacement are under investigation neonatal screening and novel metabolic modulators Which Reduce the production or toxicity of branched-chain amino acids (BCAAs: leucine, isoleucine, valine) and their keto-acids.

- Enhance residual BCKDH enzyme activity.
- Mitigate downstream effects like oxidative stress, mitochondrial dysfunction, neurotoxicity, or energy deficits helps in better management.

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