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Letter to Editor

Maple Sirup Disease in Childhood: Present Therapy Options and Gene Therapy Research

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Classic maple syrup disease presents in the first few days of life with poor feeding and lethargy, followed by worsening encephalopathy with lethargy, intermittent apnea, stereotypical movements and opisthotonos [1]. Coma and central respiratory failure occur seven to ten days after birth. The intermediate form is similar to the classic form but may start later and show less severe symptoms. Patients with the intermittent type are asymptomatic at birth but may experience episodes of acute decompensation or neurological symptoms and developmental delay during childhood. The thiamine-responsive form clinically resembles the intermediate form, with thiamine therapy improving tolerance to leucine in the diet. Maple syrup urine disease is caused by mutations in the genes for the E1a, E1b, and E2 subunits of the BCKAD, the branched chain 2-ketoacid dehydrogenase complex, which are involved in the second enzymatic step of the breakdown of the branched-chain amino acids leucine, isoleucine, and valine [2,3]. The BCKAD complex has four subunits: E1a, E1b, E2, and E3, encoded by the genes BCKDHA on chromosome 19q13.1-q13.2, BCKDHB on 6q14.1, DBT on 1p31, and DLD on 7q31-q32 [1,3,4].

Mutations in these genes lead to the accumulation of branched-chain amino acids and their branched-chain alpha-ketoacids 1,2. Maple Syrup Urine Disease (MSUD) is an autosomal recessive inherited disorder that causes disruptions in amino acid metabolism. The disease is rare with a prevalence of 1:150000-216000, but clusters have been observed in Georgia with a prevalence of 1:123000 and especially among Mennonites in Pennsylvania (1:760). Three genes are currently known to lead to the disease through mutations, resulting in Type Ia, Type Ib, and Type II. Mutations in the BCKDHA gene on chromosome 19 (19q13.2) cause Type Ia, while mutations in the BCKDHB gene on chromosome 6 (6q14.1) cause Type Ib. Type II involves a mutation in the DBT gene on chromosome 1 (1p21.2). These genes encode two enzymatically active subunits of the branched-chain alpha-keto acid dehydrogenase complex, necessary for breaking down the amino acid's leucine, isoleucine, and valine. If the third subunit of the complex, dihydrolipoyl dehydrogenase, is defective, a more severe Type III of the disease occurs, known as Dihydrolipoamide Dehydrogenase Deficiency (DLDD). This leads to the accumulation of amino acids and their byproducts in the blood and urine, causing metabolic imbalances and other complications. Infants with MSUD may exhibit symptoms like feeding difficulties, apathy, muscle stiffness, seizures, and a distinct sweet-smelling urine resembling maple syrup. If left untreated, the disease can lead to severe brain damage and death. MSUD can manifest in different forms, ranging from classic to thiamine-dependent, each with varying enzyme activity levels and clinical outcomes. Diagnosis can be made through prenatal testing or newborn screening using mass spectrometry. Treatment involves dietary restrictions and, in severe cases, interventions to manage metabolic imbalances. Treatment options include liver transplantation to restore amino acid metabolism or conservative approaches like protein-restricted diets and acute detoxification methods.

Long-term management involves monitoring amino acid levels and adhering to dietary restrictions. Research is ongoing to explore alternative treatment methods, such as gene therapy, to improve outcomes for individuals with MSUD. In maple sirup disease core lifelong therapies are divided from emerging and advanced therapies. Core lifelong therapies include dietary restrictions with limiting natural protein intake, here food with high leucine, isoleucine and valine levels. Formula, that are specialized using a BCAA-free metabolic formula are necessary to provide important nutrients like vitamins and minerals. Frequently measurement of BCAA levels in a tolerable range are necessary over long-time. Emergency protocols are necessary to have a plan for possible metabolic crisis to urgently lower BCAA levels. Emergency and advanced therapies include liver transplantation, which when successful, can remove the patient from dietary restrictions and present crisis. Pharmacological targets include investigational treatments like sodium phenylbutyrate to reduce BCAA levels. Oral enzyme therapies were developed to lower leucine levels in the gut before it enters the blood.

Gene therapies are focusing on curing the disease by repairing the responsive gene at the DNA/RNA level and to ameliorate the range of enzyme deficiency. There are many different clinical trials ongoing to date. Greig, et al. published in 2021 a muscle-directed AAV gene therapy that rescued the maple syrup urine disease phenotype in a mouse model [5]. In 2022, Pontoizeau and his team developed a liver-directed Adeno-Associated Virus (AAV8) gene therapy for MSUD [6]. Recently, published in 2025, BCKDHA-BCKDHB digenic gene therapy was introduced in two mouse models and a calf with classic maple syrup urine disease successfully [7]. Gene therapeutical approaches are still in infancy shoes and were evaluated to date in animal studies. Further ongoing research must include Phase 1-3 studies to develop approved and effective gene therapy options in children with curing aspect. Further intensive research is necessary to finalize these efforts to cure children with rare maple sirup disease [8-12].

Acknowledgment

None.

Conflict of Interest

None.

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