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A detailed summary of maple syrup urine disease

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Abstract

Maple syrup urine disease (MSUD), also known as branched-chain ketoaciduria, is a rare and inherited metabolic disorder characterized by the inability to effectively metabolize branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine. This genetic disorder is inherited in an autosomal recessive manner, with mutations in specific genes impairing the activity of enzymes responsible for BCAA breakdown. MSUD leads to the accumulation of these amino acids in the blood and tissues, resulting in a range of clinical manifestations. Early onset of an acute encephalopathy in the newborn period, characterized by lethargy, hypertonia, poor feeding, and ketoacidosis, necessitates prompt treatment to avoid lifelong neurological damage or even death. Effective dietary regulation of the BCAAs can be associated with appropriate growth; nevertheless, acute decompensation due to acute dietary protein loading, catabolic protein insults related to other chronic diseases, infection, exercise, injury, and physiological stress must be managed on a continuous basis. The effects of infants delivered to women with MSUD necessitate strict nutritional monitoring throughout pregnancy. Liver transplantation has proven to be beneficial. This paper provides a comprehensive overview of MSUD, emphasizing the clinical manifestations, genetic basis, and management strategies for this rare metabolic disorder.

Keywords: Maple Syrup Urine Disease; Management; Diagnosis; Pathophysiology

1. Introduction

Maple syrup urine disease (MSUD), also known as branched-chain ketoaciduria, is an aminoacidopathy due to an enzyme defect in the catabolic pathway of the branched-chain amino acids leucine, isoleucine, and valine. This condition is named after the characteristic sweet, maple syrup-like odour of the urine in affected individuals, which is one of the prominent symptoms. Accumulation of these 3 amino acids and their corresponding alpha-keto acids leads to encephalopathy and progressive neurodegeneration in untreated infants. Early diagnosis and dietary intervention prevent complications and may allow for normal intellectual development. [1]

2. Epidemiology

Maple syrup urine disease is a rare, inherited metabolic disorder, affecting an estimated 1 in 86,800 to 185,000 infants worldwide. Maple syrup urine disease involves males and females equally. The prevalence of MSUD is 1 in 100,000 in India. Its prevalence in the United States population is approximately 1 newborn out of 180,000 live births. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder. Due to this “founder effect”, the disorder occurs with greater frequency among individuals in the Mennonite populations in the United States, where the incidence is estimated to be as high as in 1 in 380. MSUD occurs in the Ashkenazi Jewish population with an incidence estimated at 1:26,000 live births. [2]

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3. Clinical presentation

The clinical presentation of an infant/child with maple syrup urine disease varies. Five distinct clinical phenotypes can be distinguished based on age of onset, severity of clinical symptoms, and response to oral thiamine treatment. These types of maple syrup urine disease include classic, intermediate, intermittent, thiamine-responsive, and E3-deficient. [3]

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. In the classic type, neurological signs (eg, muscular hypotonia and/or hypertonia, dystonia, seizures, encephalopathy) rapidly develop. Signs of pseudotumor cerebri may be observed, and acute transient ataxia has been reported. Pancreatitis has been occasionally reported. Ketosis and the characteristic urine odour of maple syrup are usually present when the first symptoms develop. Interestingly, this characteristic urine odour has been reported in healthy infants not affected with maple syrup urine disease.

Intermediate maple syrup urine disease is a variant of classic maple syrup urine disease and is less common than classic maple syrup urine disease; approximately 20 patients have been reported with this phenotype. 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. Clinical signs in these patients include neurological impairment, developmental delay of varying degree, and seizures. Presentation may occur at any age, depending on residual BCKD enzyme activity; however, if the patient is ill or fasting, he or she will react in a similar way to a child with classic maple syrup urine disease and will require immediate medical intervention and care.

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). Patients have normal growth and intelligence. Symptoms may not present until age 12-24 months, usually in response to catabolic stress as due to illness or a surge in protein intake. During these episodes, the characteristic maple syrup odour becomes evident, and metabolic decompensation can occur. Ataxia, lethargy, seizures, and coma may ensue. Patients with intermittent maple syrup urine disease have died during these acute episodes when not appropriately treated.

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, which, in turn, breaks down the BCAAs. Positive clinical response to supplemental thiamine has been documented in patients and has shown improved metabolic control when moderate dietary restriction of BCAAs is also followed.

E3-deficient maple syrup urine disease (dihydrolipoamide dehydrogenase deficiency) is a very rare type of maple syrup urine disease. The clinical presentation is very similar to that of intermediate maple syrup urine disease, with the exception of early-onset lactic acidosis. These patients have combined deficiencies of the BCKD enzyme complex, pyruvate, and alpha-ketoglutarate dehydrogenases.

3.1. Etiology

MSUD is due to mutations in the genes encoding subunits E1a, E1b, and E2 of the branched chain 2-ketoacid dehydrogenase (BCKAD) complex, involved in the second enzymatic step in the degradation of the branched chain amino acids (BCAAs): leucine, isoleucine and valine. BCKAD has four subunits: E1a, E1b, E2, and E3, which are encoded by the genes BCKDHA (19q13.1-q13.2), BCKDHB (6q14.1), DBT (1p31) and DLD (7q31-q32) respectively. Mutations in these genes lead to the accumulation of BCAAs (especially leucine) and their branched-chain alpha-ketoacids. Mutations in the E3 subunit gene (DLD) are not associated with MSUD but lead to pyruvate dehydrogenase E3 deficiency (see this term). A mutation in the PPM1K gene (4q22.1) has been reported in a single case of mild intermediate MSUD. [4]

3.2. Diagnosis

Prior to the widespread availability of plasma amino acid measurement, diagnosis was frequently dependent on suggestive symptoms and scent. Affected patients are now frequently recognized by elevated plasma amino acid levels that do not have the characteristic odour. Sotolon is the compound that causes the odour of urine. Tandem mass spectrometry is used to analyze the blood of 1–2-day-old infants for maple syrup urine illness. To assess if the infant has a high amount of branched-chain amino acids, the blood concentration of leucine and isoleucine is evaluated relative to other amino acids. When the infant is 2-3 days old, the blood concentration of branched-chain amino acids such as

leucine exceeds 1000 mol/L, and additional screening procedures are used. Instead, the newborn's urine is analyzed for levels of branched-chain alpha-hydroxyacids and alpha-ketoacids. [5]

3.3. Pathophysiology

Branched-chain ketoacid dehydrogenase (BCKAD) is located within the inner mitochondrial membrane of various tissues such as skeletal muscle, liver, kidney, and the brain. It is composed of three catalytic subunits (E1, E2, and E3). Together with branched-chain amino acid transaminase, it helps mediate catabolism of branched-chain amino acids (BCAA). In the presence of thiamine pyrophosphate, E1 decarboxylates the alpha ketoacids. The lipoic acid residue in E2 transfers the acyl group from E1 to CoA. The E3 subunit helps reoxidize the lipoic acid residue in E2. The activity of branched-chain ketoacid dehydrogenase is further regulated by BCKAD phosphatase and BCKAD kinase. Therefore, within the mitochondria, branched-chain amino acids are first converted into their respective alpha-ketoacids by the enzyme branched-chain amino acid transaminase. Their respective yielded alpha-ketoacids include alpha-ketoisocaproic acid, alpha-keto-beta-methyl valeric acid, and alpha-ketoisovaleric acid. Alpha-ketoacids are then oxidatively decarboxylated by the branched-chain ketoacid dehydrogenase complex. Consequently, alpha-ketoacids are further metabolized into intermediates such as isovaleryl-coenzyme A, alpha-methylbutyryl-CoA, and isobutyrl-CoA. These intermediates are then converted into succinyl-CoA, acetoacetate, and acetyl-CoA. The branched-chain amino acids are essential amino acids with hydrophobic side chains and are found in protein-rich food. The catabolism of these amino acids is necessary to maintain various physiologic functions such as Protein synthesis, Gluconeogenesis, Fatty acid synthesis, cholesterol synthesis and Cellular signaling

In the brain, BCKAD helps metabolize BCAA to facilitate cerebral GABA and glutamate synthesis. The liver and kidney are responsible for the catabolism of 10% to 15% of BCAA. Most BCAA transamination and oxidation occur in the skeletal muscle. Maple syrup urine disease occurs due to a pathogenic defect in any BCKAD subunit resulting in elevated branched-chain amino acids and their corresponding alpha keto-acids. Accumulated BCAA and alpha-ketoacids manifests as a constellation of clinical symptoms due to dysfunction of the central nervous system, immune system, and skeletal muscle. Elevated leucine and alpha-ketoisocaproic acid levels notoriously cause neurochemical disturbances resulting in clinically apparent neurotoxicity. The transport of large neutral amino acids across the blood-brain barrier is drastically reduced due to interference from elevated leucine levels. As a result, the supply of tyrosine, phenylalanine, methionine, tryptophan, histidine, and valine to the brain. As a consequence, brain growth and myelin synthesis are negatively impacted. The restricted supply of the amino acids leads to decreased neurotransmitters, such as dopamine, serotonin, norepinephrine, epinephrine, GABA, and glutamate. Alpha-ketoisocaproic acid levels of greater than 60 micromol/L negatively regulate transamination reactions within astrocytes. This reversal accounts for low cerebral glutamate levels, which results in cognitive dysfunctions such as learning disabilities and memory loss. Furthermore, elevated leucine concentrations impair cell volume regulation. This results in decreased blood osmolarity, sodium concentrations, and increased intracellular water leading to cerebral edema. In infants and children, decreased blood osmolarity can further precipitate brain herniation. Clinical evidence suggests that the neurotoxin alpha-ketoisocaproic acid contributes to the encephalopathic syndrome. In patients with classic MSUD, decreased levels of glutamate and increased cerebral lactate levels indicate inhibition of the respiratory chain by alpha-ketoisocaproic acid. The metabolic decompensations in MSUD lead to the activation of matrix metalloproteinases, resulting in the blood-brain barrier's breakdown. Isoleucine metabolites are responsible for the maple syrup odor of the urine. [6]

3.4. Management

3.4.1. Monitoring

Keeping MSUD under control requires careful monitoring of blood chemistry, both at home and in a hospital setting. DNPH or specialized dipsticks may be used to test the patient's urine for ketones (a sign of metabolic decompensation), when metabolic stress is likely or suspected. Fingerstick tests are performed regularly and sent to a laboratory to determine blood levels of leucine, isoleucine, and valine. Regular metabolic consultations, including blood-draws for full nutritional analysis, are recommended; especially during puberty and periods of rapid growth. MSUD management also involves a specially tailored metabolic formula, a modified diet, and lifestyle precautions such as avoiding fatigue and infections, as well as consuming regular, sufficient calories in proportion to physical stress and exertion. Without sufficient calories, catabolism of muscle protein will result in metabolic crisis. Those with MSUD must be hospitalized for intravenous infusion of sugars and nasogastric drip-feeding of formula, in the event of metabolic decompensation, or lack of appetite, diarrhea or vomiting. Food avoidance, rejection of formula and picky eating are all common problems with MSUD. Some patients may need to receive all or part of their daily nutrition through a feeding tube. [7]

3.4.2. Toxin removal

Following diagnosis, rapid removal of excess leucine from the body reduces the impact of the disease on development. Exchange transfusion, hemodialysis, or hemofiltration may be used.

3.4.3. Diet control

A diet with carefully controlled levels of the amino acids leucine, isoleucine, and valine must be maintained at all times in order to prevent neurological damage. Since these three amino acids occur in all-natural protein, and most natural foods contain some protein, any food intake must be closely monitored, and day-to-day protein intake calculated on a cumulative basis, to ensure individual tolerance levels are not exceeded at any time. As the MSUD diet is so protein-restricted, and adequate protein is a requirement for all humans, tailored metabolic formula containing all the other essential amino acids, as well as any vitamins, minerals, omega-3 fatty acids and trace elements (which may be lacking due to the limited range of permissible foods), are an essential aspect of MSUD management. These complement the MSUD patient's natural food intake to meet normal nutritional requirements without causing harm.[11] If adequate calories cannot be obtained from natural food without exceeding protein tolerance, specialized low protein products such as starch-based baking mixtures, imitation rice and pasta may be prescribed, often alongside a protein-free carbohydrate powder added to food and/or drink, and increased at times of metabolic stress. MSUD patients with thiamine- responsive MSUD can have a higher protein intake diet with administration of high doses of thiamine, a cofactor of the enzyme that causes the condition. The typical dosage amount of thiamine-responsive MSUD depends on the enzyme activity present and can range from 10 mg - 100 mg daily.

3.4.4. Liver transplantation

Usually MSUD patients are monitored by a dietitian. Liver transplantation is a treatment option that can completely and permanently normalize metabolic function, enabling discontinuation of nutritional supplements and strict monitoring of biochemistry and caloric intake, relaxation of MSUD-related lifestyle precautions, and an unrestricted diet. This procedure is most successful when performed at a young age, and weaning from immunosuppressants may even be possible in the long run. However, the surgery is a major undertaking requiring extensive hospitalization and rigorous adherence to a tapering regimen of medications. Following transplant, the risk of periodic rejection will always exist, as will the need for some degree of lifelong monitoring in this respect. Despite normalizing clinical presentation, liver transplantation is not considered a cure for MSUD. The patient will still carry two copies of the mutated BKAD gene in each of their own cells, which will consequently still be unable to produce the missing enzyme. They will also still pass one mutated copy of the gene on to each of their biological children. As a major surgery the transplant procedure itself also carries standard risks, although the odds of its success are greatly elevated when the only indication for it is an inborn error of metabolism. In absence of a liver transplant, the MSUD diet must be adhered to strictly and permanently. However, in both treatment scenarios, with proper management, those affected are able to live healthy, normal lives without experiencing the severe neurological damage associated with the disease.

3.4.5. Pregnancy

Control of metabolism is vital during pregnancy of women with MSUD. To prevent detrimental abnormalities in development of the embryo or foetus, dietary adjustments should be made and plasma amino acid concentrations of the mother should be observed carefully and frequently. Amino acid deficiency can be detected through foetal growth, making it essential to monitor development closely.

3.5. Prognosis

MSUD will cause mortality if left untreated owing to central neurological function impairment and respiratory failure. Early identification, a low-branched-chain amino acid diet, and thorough monitoring of blood chemistry can result in a favourable prognosis with few or no aberrant changes. The average intellectual development of the population is lower, and the severity of the deficit is proportional to the length of time the problem went untreated and the effectiveness of nutritional control, even during metabolic crises. [8]

4. Conclusion

Early detection and ongoing medical management are critical in preventing serious neurological deficits and increasing the quality of life for people with MSUD.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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