Chapter 38
Maple Syrup Urine Disease

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Maple syrup urine disease (MSUD) is a heterogeneous genetic disorder resulting from over 50 known mutations that impair the mitochondrial branched-chain α-ketoacid dehydrogenase (BCKD) complex.[1] The components of the BCKD complex include E1, a decarboxylase; E2, an acyl transferase; and E3, a lipomide dehydrogenase (dihydrolipoyl dehydrogenase). The defect in this multienzyme complex results in accumulation of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine and their respective α-ketoacids (BCKAs) in body fluids (Fig. 38–1).

Maple syrup urine disease is inherited as an autosomal recessive trait. Its incidence varies with the population studied, from 1/760 in selective screening of an inbred Mennonite group to 1/290,000 in a New England newborn screening program.[2,3] Molecular mutation analysis has not revealed a strong genotype-phenotype correlation to date. Numerous variant forms of MSUD resulting in a spectrum of BCKD insufficiency (3% to 40% normal) have been reported. The clinical outcome appears to be associated with the age at diagnosis, the degree of enzyme impairment, the time at which diet therapy is begun, and the degree of metabolic control.[4] Five clinical and biochemical phenotypes have been reported and used based on clinical presentation and therapeutic responses to thiamin observed in patients.[5]

The disease was first described in 1954 by Menkes, Hurst, and Craig, who observed four infants with progressive neurological disease associated with a maple syrup odor of the urine in the first weeks of life.[6] In 1960, Dancis et al. demonstrated that the defect was at the enzymatic level of the decarboxylation of the BCAA.[7] Infants with MSUD may appear normal after birth; however, within a few hours to days, elevations in leucine can be observed and associated with progressive neurological deterioration and possibly a maple syrup odor of the urine and sweet earwax. The clinical symptoms may include poor sucking, irregular respiration, rigidity alternating with periods of flaccidity, opisthotonos, progressive loss of Moro reflex, and seizures. Symptoms can progress to apnea and coma. Death ensues unless rigorous treatment is implemented. Early diagnosis and treatment may prevent complications and may result in normal growth and development.

Clinical and Biochemical Abnormalities

Classifications of the heterogeneous forms of MSUD have been based on clinical manifestations of the forms exhibiting varying degrees of partial BCKD enzyme activity and a thiamin-responsive form [classic, intermediate, intermittent, dihydrolipoyl dehydrogenase (E3) deficiency][5] (Table 38–1).

Factors to Be Considered in Nutritional Evaluation

In classic MSUD, BCKAs are mainly derived from leucine, and the activity of the BCKD complex in skin fibroblasts or lymphoblast cultures is usually less than 2% of normal. Clinical symptoms such as lethargy, poor sucking, the neurological signs of alternating hypertonia and hypotonia, dystonia, seizures, and encephalopathy develop and progress rapidly within a few days of life. Dietary BCAA tolerance is usually very low in this group, and symptoms typically develop between 4 and 7 days of age. Even with treatment, the outcome of patients in this group is not very satisfactory with regard to normal neonatal growth and development.[8–10] Pancreatitis has also been reported in patients with MSUD.[11,12]

Patients with the intermediate form of MSUD have greater residual enzyme activity than those with the classic form (3% to 30% of normal) and are less prone to metabolic decompensations. Patients with the intermediate form have persistent elevations of BCAA. However, their BCAA tolerance is much higher than that of patients with classic MSUD. Although such patients tolerate greater amounts of dietary leucine, dietary management similar to that for classic MSUD is required. The onset of symptoms is variable and usually precipitated by the stress of infections, surgery, trauma, or excessive protein intake. Some patients have shown larger excretion of isoleucine BCKA derivatives compared to the leucine BCKA seen in classic MSUD.[13,14] Mental delays and spasticity have been reported as clinical features often due to delayed diagnosis and management.[13,15–17]

Patients with intermittent forms of MSUD generally demonstrate normal early growth and development. The BCKD complex enzyme activity is reportedly 5% to 20% of normal.[5] The BCAAs are within the normal range when the patient is asymptomatic. However, during metabolic decompensation associated with catabolic shocks or illness, fasting, infections, or surgery, the patient may display clinical symptoms and elevated BCAAs, which are characteristic of MSUD. These episodes may be associated with progressive changes associated with acute behavioral changes and unsteady gait progressing to seizures, coma, and even death.[18,19] In this form, initial symptoms generally present between 5 months and 2 years of age, often precipitated by episodic metabolic decompensation.

Patients with thiamin-responsive MSUD usually have a clinical presentation similar to that of patients with the intermediate form with the absence of acute neonatal illness. The lack of controlled clinical trials evaluating thiamine administration has limited the establishment of clear criteria for thiamin-responsive MSUD. Pharmacological doses of 100–1000 mg/day have been used to reduce BCKA excretion and plasma BCAA and BCKA concentrations, maximally after approximately 3 weeks.[20,21] The

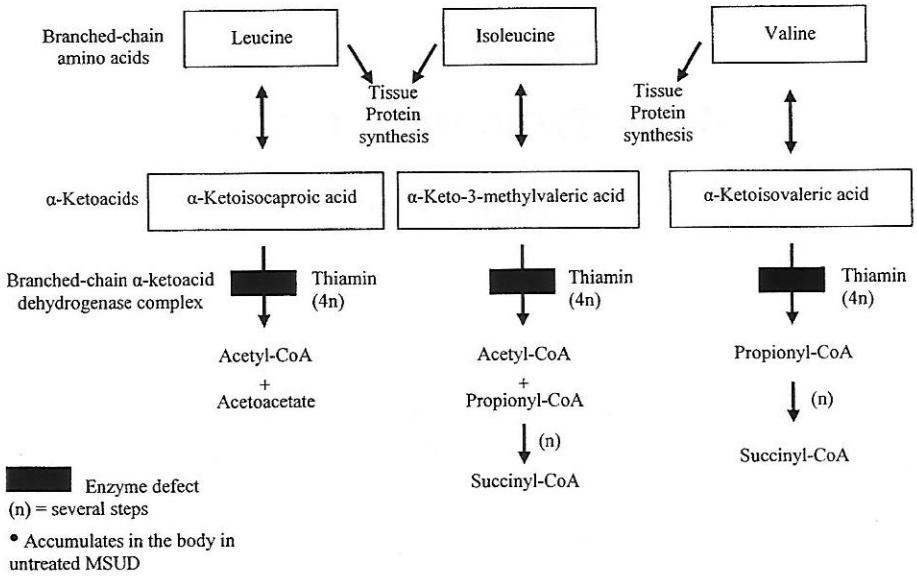

Figure 38–1. Metabolic Pathways in the catabolism of leucine, isoleucine, and valine demonstrating the site of the defect in maple syrup urine disease (MSUD). CoA, coenzyme A.

model proposed by Elsas and Danner suggests that the biological half-life of the enzyme BCKD complex is prolonged and the overall activity is increased when the binding site of the decarboxylase (E1-alpha) component becomes saturated with thiamin, resulting in a conformational change and resistance to degradation.[20] All patients with this form of MSUD have required thiamin treatment in conjunction with the diet therapy to normalize plasma BCAA levels.

Dihydrolipoyl dehydrogenase (E3)–deficient MSUD is a rare form of MSUD, with fewer than 20 patients reported in the literature.[5,22–24] The clinical presentation is similar to that of the intermediate form accompanied by lactic acidosis. Due to the combined deficiency of the BCKD, pyruvate, and α-ketoglutarate dehydrogenase complexes,[25] concentrations of lactate, pyruvate, α-ketoglutarate, α-hydroxy isovalerate, and α-hydroxyglutarate are all increased in the urine. With pyruvate accumulation, a resultant elevation in plasma alanine may be detected. Infants appear fairly normal in the first few months of life, but due to persistent lactic acidosis between 2 and 6 months, progressive neurological deterioration is observed. Treatment with pharmacological doses of thiamin, biotin, and lipoic acid, with dietary restriction of fat and BCAAs, has not produced satisfactory outcomes.[5,22,23]

Newborn diagnosis/screening for MSUD is not mandatory in all states; therefore, many infants are diagnosed after they become symptomatic. The diagnosis can be confirmed by evaluating urine BCKAs, which produce a yellow precipitate with 2–4 dinitrophenyl hydrazine (DNPH), and by quantitating plasma BCAA (leucine, isoleucine, valine) using ion-exchange chromatography. With elevated BCAA levels, the presence in the

Table 38–1. Clinical and Biochemical Phenotypes in Maple Syrup Urine Disease (MSUD)

Clinical Phenotype	Prominemt Clinical Featuers	Biochemical Features	Decarboxylation Activity % of Normal*
Classic	Neonatal onset, poor feeding, lethargy, increased/decreased tone, ketoacidosis, and seizures	Markedly increased alloisoleucine, BCAA, and BCKA	0–2
Intermediate	Failure to thrive, often no ketoacidosis, developmental delay	Persistently increased alloisoleucine, BCAA, and BCKA	3–30
Intermittent	Normal early development, episodic ataxia/ketoacidosis precipitated by infection or stress; episodes can be fatal; usually intellect is normal	Normal BCAA when asymptomatic	5–20
Thiamin-responsive	Similar to intermediate MSUD	Decreased BCKA and/or BCAA with thiamin therapy	2–40
Lipoamide dehydrogenase (E3) deficiency	Usually no neonatal symptoms, failure to thrive, hyptonia, lactic acidosis, developmental delay, movement disorder, progressive deterioration	Moderately increased BCAA, BCKA; elevated α-ketoglutarate and pyruvate	0–25

*Most commonly measured in intact peripheral blood leukocytes or cultured fibroblasts or lymphoblasts with [1-^{14}C]-labeled branched-chain amino acids (BCAA) or branded-chain α-ketoacids (BCKA) as substrate.

plasma of alloisoleucine, a metabolite of isoleucine, is pathgnomonic for MSUD.[26] The enzyme activity can be measured in the lymphocytes or cultured fibroblasts to confirm the diagnosis.[27] Prenatal diagnosis can be performed using cultured amniotic fluid cells or chorion villus cells.[27] The unaffected carrier status in MSUD is best established by molecular techniques.

Dietary Treatment

Dietary interventions to achieve and maintain normal plasma amino acid levels appear to be best correlated with a good outcome in patients with MSUD.[28] Nutritional support should be initiated promptly to promote anabolism and to reduce BCAA levels and toxic metabolite accumulation. Initiation of a BCAA-free hypercaloric diet providing 125 to 170 kcal/kg/day and protein at 2.5 to 3.0 g/kg/day may achieve net body protein accretion and the resolution of clinical symptoms.[29] Orogastric feedings are usually preferred; however, if necessary, parenteral nutrition by itself or simultaneously with BCAA-free orogastric feeds may be used to achieve anabolism. Intravenous solutions without BCAAs are now available and have been shown to be rapidly effective in correcting BCAA elevations and the related symptoms.[30,31] Immediate and short-term infusion of glucose and insulin has also been used to produce anabolism and normalize BCAAs.[32,33] However, prolonged exclusion, overrestriction, or imbalance of BCAAs leads to anemia, desquamation of the skin, diarrhea, and failure to thrive.[34–36] Emergency treatment with peritoneal dialysis using a nitrogen-free dialysate may be effective in rapidly lowering plasma BCAA and BCKA concentrations, but because it may prolong the catabolic state, the associated risks may outweigh the benefits.[37] Therefore, it is not recognized as the preferred method of treatment compared to aggressive nutrition intervention involving an increased energy-dense diet to normalize BCAAs.

The declination rate of elevated amino acids may vary due to several factors, including genotype and the amount or source of the amino acid calories. Leucine declination appears to be accelerated in patients provided medical foods supplying all essential amino acids except leucine, isoleucine, and valine. In general, plasma concentrations of isoleucine and valine may decrease more rapidly than leucine concentrations, possibly declining to subnormal levels while leucine levels remain high.[38] In these conditions, adding L-isoleucine and L-valine to medical foods prevents catabolism and normalizes all plasma amino acids, possibly by, in part, restoring the limited amino acid substrate required for normal rates of protein synthesis.

Long-term treatment of MSUD involves lifelong dietary therapy to maintain plasma BCAAs within the therapeutic range while promoting normal growth and development. This involves careful titration of protein from several commercial BCAA-free medical foods and essential BCAA from standard formulas for infants and natural foods in older patients with plasma BCAA.

The daily BCAA requirements vary with age, severity of the enzyme defect, and growth rate.[5] The suggested range of intake of these nutrients for individuals with MSUD is outlined in Table 38–2. Children and adolescents with MSUD tolerate 300–600 mg leucine per day. Frequent adjustments of the dietary prescription, along with monitoring of plasma BCAA and urinary BCAA and BCKA, are therefore necessary. Adequate protein and calorie intake is possible through the use of medical foods and a wide variety of low-protein foods. Medical foods with different nutrient compositions and forms are now available, which include BCAA-free modules only or in combination with carbohydrates or fats in the form of powders, capsules, or bars. Therefore, a complete diet analysis to assess adequate nutrient intake is essential. Maple syrup urine disease food lists to count leucine and protein contents are now available.[39] Foods with similar leucine content (30 mg) are categorized in different food groups.

Table 38–2. Recommended Daily Nutrient Intakes for Infants and Children with Maple Syrup Urine Disease

	Age						
Nutrient*	<6 mo	6 to 12 mo	1 to 4 yr	4 to 7 yr	7 to 11 yr	11 to 15 yr	15 to 19 yr
Energy (kcal/kg)	115–120 (95–145)	105–110 (80–135)					
(kcal/day)			1300 (900–1800)	1700 (1300–2300)	2400 (1650–3300)	2200–2700 (1500–3700)	2100–2800 (1200–3900)
Protein							
(g/kg)	3.0–3.5	2.5–3.0					
(g/day)			≥30	≥35	≥40	≥50–55	≥55–65
Carbohydrate							
(% of kcal)	35%	35%	35%	50%	50%	50%	50%
Fat							
(% of kcal)	50%	50%	50%	35%	35%	35%	35%
Isoleucine†							
(mg/kg/day)	30–60	18–40					
(mg/day)			165–325	215–420	245–470	325–345	330–570
Leucine							
(mg/kg/day)	50–100	30–70					
(mg/day)			275–535	360–695	410–785	540–740	550–945
Valine‡							
(mg/kg/day)	35–70	21–50					
(mg/day)			190–400	250–490	285–550	375–520	385–665

*Nutrient levels as described in reference 29.
†Generally recommended to provide isoleucine at approximately 60% of the leucine prescription.
‡Generally recommended to provide valine at approximately 70% of the leucine prescription.

In patients having common illnesses, infections, or surgeries, MSUD, if left untreated, may result in serious consequences such as coma and death. It becomes essential to decrease leucine and increase calorie and fluid intake to prevent catabolism. If a child cannot tolerate oral feedings during illness, hospitalization may be necessary to provide nutritional support intravenously. Acute episodes, which are usually associated with ketoacidosis, require large amounts of parenteral fluids and electrolytes to prevent catabolism. There are a few published reports indicating that appropriate nutritional management during pregnancy in women with MSUD can result in successful pregnancy outcomes.[40,41] The available data suggest that a critical aspect of nutritional intervention is preserving maternal anabolism during delivery and immediately postpartum for an optimal outcome.[40,41]

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