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NLM Citation: Strauss KA, Puffenberger EG, Carson VJ. Maple Syrup Urine Disease. 2006 Jan 30 [Updated 2020 Apr 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Maple Syrup Urine Disease

Synonyms: BCKD Deficiency, Branched-Chain Ketoacid Dehydrogenase Deficiency, Maple Syrup Disease, MSUD

Kevin A Strauss, MD,[1] Erik G Puffenberger, PhD,[1] and Vincent J Carson, MD[1]

Created: January 30, 2006; Updated: April 23, 2020.

Summary

Clinical characteristics

Maple syrup urine disease (MSUD) is categorized as classic (severe), intermediate, or intermittent. Neonates with classic MSUD are born asymptomatic but without treatment follow a predictable course:

- **12–24 hours.** Elevated concentrations of branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) and alloisoleucine, as well as a generalized disturbance of amino acid concentration ratios, are present in blood and the maple syrup odor can be detected in cerumen;
- **Two to three days.** Early and nonspecific signs of metabolic intoxication (i.e., irritability, hypersomnolence, anorexia) are accompanied by the presence of branched-chain alpha-ketoacids, acetoacetate, and beta-hydroxybutyrate in urine;
- **Four to six days.** Worsening encephalopathy manifests as lethargy, apnea, opisthotonos, and reflexive "fencing" or "bicycling" movements as the sweet maple syrup odor becomes apparent in urine;
- **Seven to ten days.** Severe intoxication culminates in critical cerebral edema, coma, and central respiratory failure.

Individuals with intermediate MSUD have partial branched-chain alpha-ketoacid dehydrogenase deficiency that manifests only intermittently or responds to dietary thiamine therapy; these individuals can experience severe metabolic intoxication and encephalopathy in the face of sufficient catabolic stress. In the era of newborn screening (NBS), the prompt initiation of treatment of asymptomatic infants detected by NBS means that most individuals who would have developed neonatal manifestations of MSUD remain asymptomatic with continued treatment adherence.

Diagnosis/testing

Suggestive biochemical findings on NBS include whole-blood concentration ratios of (leucine + isoleucine) to alanine and phenylalanine that are above the cutoff values for the particular screening lab. Follow-up plasma

Author Affiliation: 1 Clinic for Special Children, Strasburg, Pennsylvania; Email: kstrauss@clinicforspecialchildren.org; Email: epuffenberger@clinicforspecialchildren.org; Email: vcarson@clinicforspecialchildren.org.

amino acid analysis typically demonstrates elevated concentrations of BCAAs and alloisoleucine. The diagnosis of MSUD is confirmed by identification of biallelic pathogenic variants in *BCKDHA*, *BCKDHB*, or *DBT*.

Management

Treatment of manifestations: Treatment consists of dietary leucine restriction, BCAA-free medical foods, judicious supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring. A BCAA-restricted diet fortified with prescription medical foods can maintain average plasma BCAA concentrations within standard reference intervals and preserves the ratios among them. Use of a "sick-day" formula recipe (devoid of leucine and enriched with calories, isoleucine, valine, and BCAA-free amino acids) combined with rapid and frequent amino acid monitoring allows many catabolic illnesses to be managed in the outpatient setting. Acute metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to achieve sustained net protein synthesis in tissues. Some centers use hemodialysis/hemofiltration to remove BCAAs from the extracellular compartment, but this intervention does not alone establish net protein accretion. Brain edema is a common complication of metabolic encephalopathy and requires careful management in an intensive care setting. Adolescents and adults with MSUD are at increased risk for attention-deficit/hyperactivity disorder, depression, and anxiety disorders and can be treated successfully with standard psychostimulant and antidepressant medications.

Prevention of primary manifestations: Transplantation of allogeneic liver tissue affords affected individuals an unrestricted diet and protects them from metabolic crises, but does not reverse preexisting psychomotor disability or mental illness. In those who have not undergone liver transplantation, strict and consistent metabolic control can decrease the risk of developing neuropsychiatric morbidities. Consider a trial of enteral thiamine to determine if an affected individual may have thiamine-responsive disease.

Prevention of secondary complications: Any trauma care or surgical procedures should be approached in consultation with a metabolic specialist.

Surveillance: Weekly or twice-weekly assessment of amino acid profile for rapidly growing infants; weekly amino acid profile assessment in children, adolescents, and adults; routine monitoring of calcium, magnesium, zinc, folate, selenium, and omega-3 essential fatty acid levels; at least monthly visit with a metabolic specialist in infancy; assessment of developmental milestones at each visit or as needed.

Evaluation of relatives at risk: It can be determined if newborn sibs of an affected individual (who have not been tested prenatally) are affected (1) by plasma amino acid analysis at approximately 24 hours of life; or (2) by molecular genetic testing of umbilical cord blood if the family-specific pathogenic variants have been identified. Early diagnosis may allow management of asymptomatic infants out of hospital by experienced providers. Before confirmatory molecular testing is complete, at-risk neonates can be managed with an MSUD prescription diet if serial plasma amino acid profiles provide evidence of MSUD.

Pregnancy management: For women with MSUD, metabolic control should be rigorously maintained before and throughout pregnancy by frequent monitoring of plasma amino acid concentrations and dietary adjustments to avoid the likely teratogenic effects of elevated maternal leucine plasma concentration. Fetal growth should be monitored to detect any signs of essential amino acid deficiency. The catabolic stress of labor, involutional changes of the uterus, and internal sequestration of blood are potential sources of metabolic decompensation of the affected mother. Appropriate monitoring of the affected mother at a metabolic referral center at the time of delivery and in the postpartum period are recommended.

Genetic counseling

MSUD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being unaffected and a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants have been identified in an affected family member.

Diagnosis

Maple syrup urine disease (MSUD) is caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex (BCKD), the second enzymatic step in the degradative pathway of the branched-chain amino acids (BCAAs), which includes leucine, isoleucine, and valine.

Scenario 1. Abnormal newborn screening (NBS) result

- NBS for MSUD is primarily based on quantification of the ratios of (leucine + isoleucine) to alanine and phenylalanine concentrations on dry blood spots.
- A positive screening value (i.e., those above the cutoff reported by the screening laboratory) require follow-up biochemical testing with quantitative plasma amino acid and alloisoleucine analyses. If either is abnormal, treatment (see Management) and testing to establish the diagnosis (see Establishing the Diagnosis) should be initiated concurrently.

  Note: Individual states set standards for positive or suspected positive screens.
- Because leucine-isoleucine and hydroxyproline cannot be differentiated by mass spectrometry, neonates with isolated hydroxyprolinemia will screen positive for MSUD, but confirmatory amino acid analysis will show only increased hydroxyproline (a false positive newborn screening result).
- Neonates and infants suspected of having MSUD should never be challenged with higher than normal protein intake during the diagnostic process (see Management). This practice is dangerous; modern diagnostic methods make it unnecessary.

Scenario 2. A symptomatic individual with either atypical findings or untreated infantile-onset MSUD (resulting from any of the following: NBS not performed, false negative NBS result, or caregivers not adherent to recommended treatment following a positive NBS result)

Supportive clinical and laboratory findings can include the following.

Clinical findings

- Untreated infant:
  - Maple syrup odor in cerumen, the first clinical sign of MSUD, is detectable 12 hours after birth.
  - Signs of deepening encephalopathy including lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" are evident by age four to five days.
  - Coma and central respiratory failure may occur by age seven to ten days, sometimes before newborn screening results are available.
- Untreated older individuals with milder variants of MSUD:
  - Anorexia
  - Poor growth
  - Irritability
  - Developmental delays later in infancy or childhood
  - Acute hyperleucinemia, ketonuria, and encephalopathy if stressed by fasting, dehydration, or infectious illness

Laboratory findings

- Elevated plasma concentrations of BCAAs and alloisoleucine
- Urinary excretion of BCKDs and branched-chain alpha-ketoacids (BCKAs) in infants older than 48-72 hours on an unrestricted diet
- Ketonuria detected by standard urine test strips

  Ketonuria in a newborn should always prompt investigation for metabolic disorders.
- Absence of hypoglycemia and hyperammonemia

Establishing the Diagnosis

The diagnosis of MSUD in a proband with suggestive metabolic/biochemical findings **is established** by identification of biallelic pathogenic (or likely pathogenic) variants in one of the genes listed in Table 1 or – in limited instances – by significantly reduced activity of the BCKD enzyme in cultured fibroblasts, leukocytes, or biopsied liver tissue. Because of its relatively high sensitivity, molecular genetic testing can obviate the need for enzymatic testing and, thus, is increasingly the preferred confirmatory test for MSUD.

Note: (1) In vitro measurements of BCKD activity do not correlate with measurements of in vivo leucine oxidation [Schadewaldt et al 2001], dietary leucine tolerance [Strauss et al 2010], or in vivo response to BCKD-activating medications [Brunetti-Pierri et al 2011]. Therefore, the authors do not find measurements of BCKD enzyme activity clinically useful. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

Molecular Genetic Testing Approaches

Scenario 1. Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of MSUD, the preferred molecular genetic testing approach is use of a **multigene panel** that contains *BCKDHA*, *BCKDHB*, and *DBT*. In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

- Sequence analysis detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.
- For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Scenario 2. A symptomatic individual with atypical findings or untreated infantile-onset MSUD (resulting from NBS not performed or false negative NBS result). When the diagnosis of MSUD has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Maple Syrup Urine Disease

Gene [1, 2]	Proportion of MSUD Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
BCKDHA	45%	~92%	~8% [6, 7]
BCKDHB	35%	~93%	~7%
DBT	20%	~86%	~14% [8]
Unknown [9, 10]		NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
6. Quental et al [2008]
7. Rodríguez-Pombo et al [2006]
8. Herring et al [1992]
9. Inactivating variants of *BCKDK* in humans are associated with BCAA deficiency, autism, epilepsy, and intellectual disability that may respond to dietary treatment [Novarino et al 2012].
10. Defects of *PPM1K* may account for a subset of human MSUD but to date no cases have been reported.

Clinical Characteristics

Clinical Description

Traditionally, the metabolic phenotype of maple syrup urine disease (MSUD) is termed classic or intermediate on the basis of residual branched-chain alpha-ketoacid dehydrogenase (BCKD) enzyme activity. Rarely, affected individuals have partial BCKD enzyme deficiency that manifests only intermittently or responds to dietary thiamine therapy (see Table 2). Phenotypic distinctions are not absolute: individuals with intermediate or intermittent forms of MSUD can experience severe metabolic intoxication and encephalopathy if physiologic stress is sufficient to overwhelm residual BCKD activity or this activity is reduced by transient changes in the phosphorylation state of the enzyme complex. Even in persons with relatively high baseline residual BCKD enzyme activity, episodes of metabolic intoxication can be fatal.

Table 2. Clinical Phenotypes of Maple Syrup Urine Disease

Type	Age of Onset [1]	Clinical Features	Biochemical Signs [2]	% with Normal BCKD Activity [3]
Classic	Neonatal	• Maple syrup odor of cerumen • Poor feeding • Irritability, lethargy • Opisthotonus • Focal dystonia • "Fencing," "bicycling" • Obtundation, coma • Central respiratory failure	• ↑ BCAAs in plasma • ↑ plasma alloisoleucine • ↑ BCKAs in urine • Ketonuria	0%-2%
Intermediate	Variable	• Maple syrup odor of cerumen • Poor growth • Poor feeding • Irritability • Developmental delays • Encephalopathy during illness	Similar to classic phenotype, though quantitatively less severe	3%-30%
Intermittent	Variable	• Normal early growth & development • Episodic decompensations that can be severe	• Normal BCAAs when well • Similar to classic biochemical profile during illness	5%-20%
Thiamine-responsive	Variable	Similar to intermediate phenotype	Improvement of leucine tolerance & biochemical profile w/thiamine therapy	2%-40%

BCAAs = branched-chain amino acids; BCKAs = branched-chain alpha-ketoacids

1. All infants with classic MSUD present during the neonatal period. For other forms, age of presentation depends on several variables, including dietary protein and calorie intake, growth rate, number and severity of infectious illnesses, and rarely, dietary thiamine intake.

2. Biochemical signs should always be interpreted in the context of dietary leucine tolerance and prevailing clinical circumstances. Dietary leucine tolerance (in mg/kg/day) is defined as the steady-state leucine intake that permits normal growth and maintains plasma leucine concentration within the normal range.

3. The authors do not rely on tissue measurements of decarboxylation activity but classify affected individuals based on their leucine tolerance and metabolic response to illness. Decarboxylation data are from Chuang & Shih [2001].

Metabolic considerations in establishing MSUD phenotype:

- **Dietary leucine tolerance.** Leucine tolerance is defined as the weight-adjusted daily leucine intake that is sufficient for normal growth and maintains plasma leucine concentration within the normal range (reference mean ±2 SDs). In persons with classic MSUD, in vivo oxidation and urinary losses of branched-chain amino acids (BCAAs) are negligible [Schadewaldt et al 1999b, Levy 2001]. Thus, leucine tolerance reflects a balance between unmeasured protein losses (e.g., sloughed skin, hair, and nails) and the net accretion of body protein, which in turn is linked to growth rate [Strauss et al 2010]. During metabolic crises, changes of plasma leucine mirror whole-body protein turnover, which can be quantified if one assumes the human body is 10%-12% protein, protein is about 10% leucine by weight, and free leucine (molecular weight 131 mg/mmol) is evenly distributed in total body water [Garrow et al 1965, Filho et al 1997].
- **Plasma concentration ratios of BCAAs.** The wild type BCKD complex maintains stringent stoichiometric relationships among the three BCAAs, such that plasma concentration ratios (µmol/L:µmol/L) of leucine to isoleucine (Leu/Iso) and valine to leucine (Val/Leu) remain close to 2.0 in diverse

physiologic contexts, including overnight fasting, protein loading, and catabolic illness. In contrast, these concentration ratios vary across several orders of magnitude in individuals with classic MSUD [Strauss et al 2006]. Individuals with intermediate forms of MSUD are less vulnerable to these volatile changes of plasma BCAA concentrations and less likely to experience prolonged essential amino acid deficiencies.

- **Plasma alloisoleucine.** Alloisoleucine is a chemical derivative of isoleucine and represents the most sensitive and specific diagnostic marker for all forms of MSUD. Plasma alloisoleucine is <5 µmol/L in healthy infants, children, and adults, and exceeds this value in 94% and 99.9% of samples from individuals with intermediate and classic forms of MSUD, respectively [Schadewaldt et al 1999a].
- **Rapidity and severity of decompensation during illness.** The risk for metabolic crisis in any ill person with MSUD depends on residual in vivo BCKD enzyme activity in relation to the net liberation of free leucine from protein catabolism. Thus, individuals with residual in vivo BCKD enzyme activity enjoy a higher leucine tolerance when well and also tend to have slower and less severe elevations of plasma leucine concentrations during illnesses.

Classic MSUD Phenotype

Maple syrup odor is evident in cerumen soon after birth and in urine by age five to seven days. In untreated neonates, ketonuria, irritability, and poor feeding occur within 48 hours of delivery. Lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" are evident by age four to five days and are followed by coma and central respiratory failure. Preemptive detection of affected newborns, before they exhibit neurologic signs of MSUD, significantly reduces lifetime risk of intellectual disability, mental illness, and global functional impairment [Strauss et al 2012, Muelly et al 2013, Strauss et al 2020].

Following the neonatal period, acute metabolic intoxication (leucinosis) and neurologic deterioration can develop rapidly at any age as a result of net protein degradation precipitated by infection, surgery, injury, or psychological stress (see Figure 1). In infants and toddlers, leucinosis causes nausea, anorexia, altered level of consciousness, acute dystonia, and ataxia. Neurologic signs of intoxication in older individuals vary and can include cognitive impairment, hyperactivity, sleep disturbances, hallucinations, mood swings, focal dystonia, choreoathetosis, and ataxia. As plasma concentrations of leucine and alpha-ketoisocaproic acid (aKIC) increase, individuals become increasingly stuporous and may progress to coma. In persons of all ages with MSUD, nausea and vomiting are common during crisis and often necessitate hospitalization [Morton et al 2002].

Each episode of acute leucinosis is associated with a risk for cerebral edema (see Figure 2) [Levin et al 1993] and death [Strauss et al 2020]. Mechanisms of brain edema in MSUD are not completely understood. Plasma leucine concentration correlates only indirectly with the degree of swelling; severe cerebral edema and neurologic impairment are more directly related to the rate of change of plasma leucine and concomitant decreases in blood osmolarity. During the evolution of leucinosis, cerebral vasopressin release may be provoked by both acute hyperosmolarity (from the accumulation of BCAAs, ketoacids, ketone bodies, and free fatty acids in the circulation) and vomiting. Renal excretion of branched-chain alpha-ketoacids (BCKAs) is accompanied by obligate urine sodium loss, and when this coincides with renal free water retention (antidiuresis), administration of hypotonic or even isotonic fluids can result in hyponatremia and critical brain edema [Strauss & Morton 2003].

Transient periods of MSUD encephalopathy appear fully reversible, provided no global or focal ischemic brain damage occurs. In contrast, prolonged amino acid imbalances, particularly if they occur during the early years of brain development, lead to structural and functional neurologic abnormalities that have morbid long-term psychomotor consequences [Carecchio et al 2011, Shellmer et al 2011, Muelly et al 2013, Strauss et al 2020].

Neonatal screening and sophisticated enteral and parenteral treatment protocols (see Management) have significantly improved neurologic outcomes for persons with classic MSUD [Strauss et al 2010, Muelly et al 2013, Strauss et al 2020], but risks of acute brain injury or death are always present, and the long-term

neuropsychiatric prognosis is guarded. In two longitudinal studies of individuals with classic MSUD [Muelly et al 2013, Strauss et al 2020], an asymptomatic neonatal course and stringent longitudinal biochemical control proved fundamental to optimizing long-term cognitive outcome and mental health.

- **Early developmental milestones.** Children with MSUD who are diagnosed during the neonatal period and managed prospectively under stringent dietary control can achieve major developmental milestones along time courses similar to their unaffected sibs [Strauss et al 2020].
- **Cognitive function.** Among individuals with classic MSUD (n = 81, ages 3.6-51.1 years), full scale intelligence quotient (FSIQ) correlates with birthdate ($r_s = 0.39$, $p = 0.0044$) and is on average 20%-40% lower in affected individuals as compared to their unaffected sibs [Strauss et al 2020]. This difference is most striking for affected individuals born before the advent of newborn screening (NBS) (FSIQ of 62 ± 17, range 40-99). FSIQ correlates directly with the frequency of amino acid monitoring and inversely with both average lifetime plasma leucine and its concentration ratio to valine [Muelly et al 2013]. Prolonged neonatal encephalopathy is the single strongest predictor of neurocognitive disability and global functional impairment [Muelly et al 2013, Strauss et al 2020].
- **Mood and anxiety.** Among individuals with classic MSUD who complete appropriate objective testing, the probability of affective illness (depression, anxiety, and panic disorder) is between 83% and 100% by age 35 years [Muelly et al 2013, Strauss et al 2020]. Newborns who were encephalopathic at the time of diagnosis are five and ten times more likely, respectively, to later suffer from anxiety and depression (see Table 3) [Muelly et al 2013].
- **Attention and hyperactivity.** Cumulative lifetime incidence of attention-deficit/hyperactivity disorder (ADHD) exceeds 50% among individuals with MSUD on dietary therapy and may be even higher among those who underwent liver transplantation [Muelly et al 2013].
- **Movement disorders.** Among 17 adults with MSUD (mean age 27.5 years), 12 (70.6%) had a movement disorder (primarily tremor, dystonia, or a combination of both) on clinical examination [Carecchio et al 2011]. Parkinsonism and simple motor tics were also observed. Pyramidal signs were present in 11 affected individuals (64.7%), and a spastic-dystonic gait was observed in six (35.2%). In the authors' experience, such motor disabilities are rare in individuals with MSUD who are managed appropriately from the neonatal period but common among those who did not have the advantage of NBS [Strauss et al 2020].

Table 3. Lifetime Relative Risk of Each Finding Based on Condition at the Time of Diagnosis

Ill vs Well at Diagnosis	Relative Risk	Fisher's Exact p
Depression	10.3	0.001
Anxiety	5.1	0.007
Global assessment of functioning <70	4.0	0.05
Full scale intelligence quotient <70	2.9	0.20
Attention-deficit/hyperactivity	1.4	0.28

Muelly et al [2013]
The relative risk in this table compares the likelihood of developing the finding if the affected individual was ill at the time of diagnosis versus if the affected individual was well at the time of diagnosis.

Liver transplantation appears to prevent catastrophic brain injuries that can occur during metabolic intoxication [Mazariegos et al 2012] and arrests the progression of neurocognitive impairment [Shellmer et al 2011], but does not reverse preexisting cognitive disability or psychiatric illness [Strauss et al 2020]. Neuropsychiatric morbidity and neurochemistry are similar among individuals with MSUD who have and have not undergone liver transplantation [Muelly et al 2013, Strauss et al 2020].

Non-central nervous system involvement in MSUD can include:

- **Iatrogenic essential amino acid deficiency.** Anemia, acrodermatitis, hair loss, growth failure, arrested head growth, anorexia, and lassitude are complications of chronic deficiency of leucine, isoleucine, or valine [Puzenat et al 2004]. Iatrogenic cerebral essential amino acid deficiency can be a cause of significant neurologic morbidity in any individual ingesting a diet low in natural protein and high in prescription medical protein [Strauss et al 2010, Manoli et al 2016].
- **Recurrent oroesophageal candidiasis.** *Candida* infections are common in hospitalized persons with MSUD and may result from T-cell inhibitory effects of elevated plasma leucine [Hidayat et al 2003] or iatrogenic immunodeficiency as a result of inadequate BCAA intake.

Intermediate MSUD

Similar principles govern the acute and chronic management of classic and intermediate forms of MSUD (see Management), and the distinction between them is not absolute (see Genotype-Phenotype Correlations) [Strauss et al 2020]. Individuals with residual BCKD activity (i.e., 3%-30% *ex vivo*) may appear well during the neonatal period but nevertheless have maple syrup odor in cerumen and a consistently abnormal plasma amino acid profile (see Table 2). Individuals with intermediate MSUD can present with feeding problems, poor growth, and developmental delay during infancy, or may present much later in life with apparently nonsyndromic intellectual disability [Chuang & Shih 2001]. The majority of persons with intermediate MSUD are detected by NBS, although detection later in childhood can occur in settings where newborns are not tested for MSUD. When followed longitudinally, individuals with intermediate forms of MSUD have plasma BCAA concentrations similar to those observed in individuals with the classic form, but tolerate more dietary leucine and require less nutritional support to reverse episodes of metabolic intoxication [Strauss et al 2020]. Children and adults with intermediate MSUD can nevertheless develop severe leucinosis and brain swelling if subjected to sufficient catabolic stress.

Intermittent MSUD

Children with the intermittent form of MSUD have normal growth and intellectual development throughout infancy and early childhood. When they are well, they generally tolerate a normal leucine intake, and plasma amino acid and urine organic acid profiles are normal or show only mild elevations of BCAAs. During infections or other physiologic stress, they can develop the clinical and biochemical features of classic MSUD, in rare cases culminating in coma and death [Chuang & Shih 2001]. These individuals may escape detection by NBS.

Thiamine-Responsive MSUD

It is not known with certainty if individuals with true thiamine-responsive MSUD exist. In general, such putative individuals have residual ex vivo BCKD enzyme activity of up to 40% normal and are not ill in the neonatal period, but present later in life with a clinical course similar to intermediate MSUD. To date, no person with "thiamine-responsive" MSUD has been treated solely with thiamine. Rather, they are treated with a combination of thiamine (doses ranging from 10 to 1,000 mg/day) and dietary BCAA restriction, making the in vivo contribution of thiamine impossible to discern [Chuang et al 2004]. Based on in vitro data, Chuang et al [2006] provided a biochemical model of thiamine responsiveness linked to specific pathogenic variants in the E2 subunit of BCKD. It is therefore reasonable to try thiamine supplementation under controlled dietary conditions in any individual with MSUD who has verified *BCKDHB* pathogenic variants.

Pathophysiology

BCKD has four subunit components (E1a, E1b, E2, and E3). Pathogenic variants in both alleles encoding any subunit can result in decreased activity of the enzyme complex and the accumulation of BCAAs and corresponding BCKAs in tissues and plasma [Nellis et al 2003, Chuang et al 2004] (see Nomenclature).

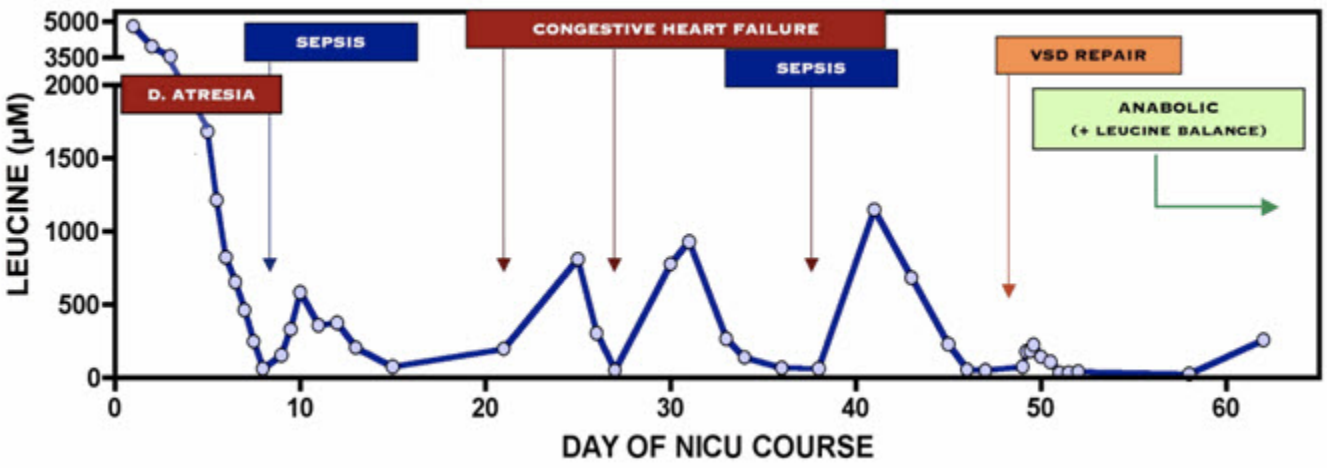

Figure 1. Serial plasma leucine measurements over a 62-day NICU course in a Mennonite newborn with trisomy 21 and classic MSUD. Plasma leucine levels rise predictably as a result of net protein catabolism provoked by a variety of physiologic stresses, including intravenous line sepsis, congestive heart failure, and ventricular septal defect repair. Each catabolic illness is treated with parenteral MSUD solution, high calorie intake, and supplemental isoleucine and valine to restore the anabolic state.

Republished with permission from Strauss et al [2010]

For more information on the pathophysiology of MSUD click here (pdf).

Genotype-Phenotype Correlations

The severity of the MSUD metabolic phenotype is determined by the amount of residual BCKD enzyme activity relative to dietary BCAA excess and the large demands for BCAA oxidation that accompany fasting, illness, or other catabolic stresses [Strauss et al 2010]. Although there are some established relationships between genotype and biochemical phenotype (i.e., classic vs intermediate), clinical and functional outcomes (e.g., FSIQ, psychiatric illness, executive dysfunction) cannot be predicted from genotype [Strauss et al 2020]. Individuals with the same MSUD genotype may vary considerably in their cerebral response to metabolic crisis – some being more vulnerable than others to the complications of metabolic encephalopathy, brain edema, and mental illness – and long-term outcomes are largely related to the timing and quality of metabolic control.

Nomenclature

Biochemical derangement caused by biallelic pathogenic variants in *BCKDHA* encoding BCKA decarboxylase (E1) alpha subunit is sometimes referred to as MSUD type 1A. Biochemical derangement caused by biallelic pathogenic variants in *BCKDHB* encoding BCKA decarboxylase (E1) beta subunit is sometimes referred to as MSUD type 1B, and biallelic pathogenic variants in *DBT* encoding dihydrolipoyl transacylase (E2) subunit are sometimes referred to as MSUD type 2. All three are clinically indistinguishable biochemically.

Note: Dihydrolipoamide dehydrogenase deficiency, caused by biallelic pathogenic variants in *DLD* encoding the E3 subunit (lipoamide dehydrogenase) of BCKD, is sometimes referred to as MSUD type 3, although the phenotype is easily distinguishable from MSUD (see Differential Diagnosis).

Prevalence

MSUD is rare in most populations, with incidence estimates of 1:185,000 live births [Chuang & Shih 2001, Nellis et al 2003].

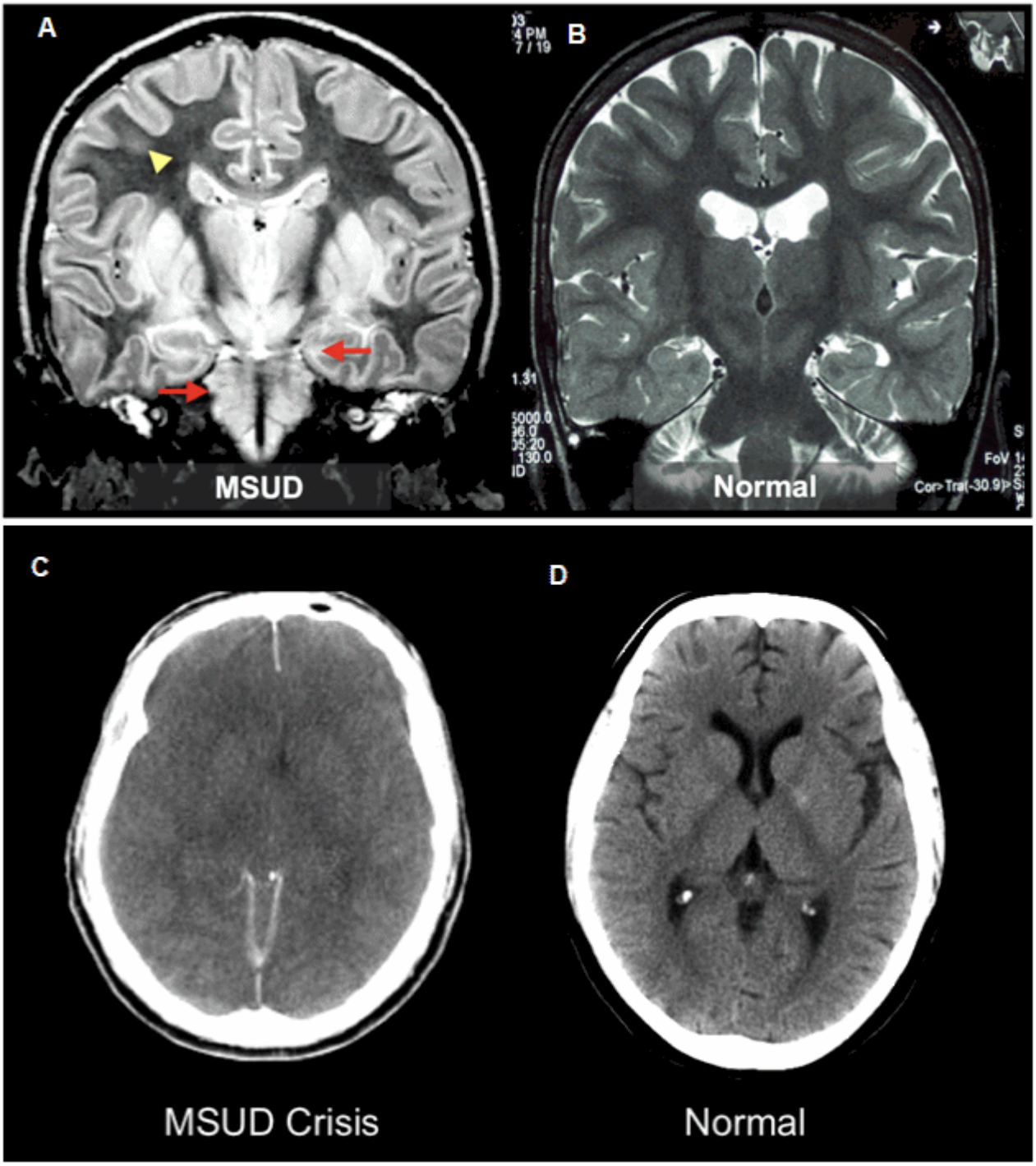

Figure 2. A. Coronal T_2-weighted MRI from a Mennonite boy age five years during an acute metabolic crisis. Diffuse gray matter swelling and signal hyperintensity (on T_2-weighted and FLAIR images) involve the cortical mantle, basal ganglia nuclei, hippocampus, and brain stem. Patches of increased T_2-weighted signal are also seen in white matter of the centrum semiovale (yellow arrowhead). Swelling of the pons and medial temporal lobes (red arrows) increases the risk for transtentorial herniation and occlusion of the posterior cerebral circulation, particularly if serum osmolarity decreases. On diffusion-weighted imaging, areas of T_2-weighted signal hyperintensity have restricted water diffusion, indicating acute cytotoxic edema. These changes are fully reversible.

B. Comparable coronal slice from a healthy age-matched individual

C. Comparable axial CT image of the brain of an individual with MSUD during crisis. Note indices of cerebral edema: apposition of cerebral tissue to the inner skull table, decreased volume of cerebral ventricles and basal fluid spaces, and reduced gray-white discrimination.

D. Comparable axial CT image of a normal brain

As a result of a founder variant (c.1312T>A) in *BCKDHA* (E1a), certain Mennonite populations of Pennsylvania, Kentucky, New York, Indiana, Wisconsin, Michigan, Iowa, and Missouri have a carrier frequency for classic MSUD as high as one in ten and a disease incidence of approximately one in 380 live births [Puffenberger 2003] (see Molecular Genetics).

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with germline pathogenic variants in *BCKDHA*, *BCKDHB*, or *DBT*.

Differential Diagnosis

Entities to exclude in the encephalopathic neonate include birth asphyxia, hypoglycemia, status epilepticus, kernicterus, meningitis, and encephalitis. The few inborn errors of metabolism that present with neonatal encephalopathy include the following:

- Hyperketosis syndromes (e.g., beta-ketothiolase deficiency [OMIM 203750])
- Urea cycle defects (See Urea Cycle Disorders Overview.)
- Glycine encephalopathy (nonketotic hyperglycinemia)
- Propionic acidemia or isolated methylmalonic acidemia (rarely)

Among these, MSUD is unique for the sweet odor of cerumen and a positive urine dinitrophenylhydrazine test. Laboratory testing that includes quantitative plasma amino acids, plasma or whole-blood alloisoleucine, serum acylcarnitines, urine organic acids, plasma ammonia concentration, and serum lactate concentration distinguishes among these possibilities. In particular, quantitative analysis of plasma amino acids is generally sufficient to diagnosis MSUD expeditiously.

4,5-dimethyl-3-hydroxy-2[5H]-furanone (sotolone), which is thought to be responsible for the characteristic odor of MSUD [Podebrad et al 1999], is also found in maple syrup, fenugreek, and lovage. Maternal ingestion of fenugreek during pregnancy has resulted in false suspicion of MSUD [Korman et al 2001]. Topical benzoin, commonly used in NICUs, also gives off a strong sweet odor.

Note: Pathogenic variants in *DLD*, the gene encoding the E3 subunit, are associated with dihydrolipoamide dehydrogenase deficiency, which produces a different phenotype. Affected infants have hypotonia, developmental delay, dystonia/chorea, and a Leigh-type encephalopathy. BCKD enzyme activity is 0%-25% of control activity. Moderate elevations of plasma concentration of BCAAs, lactic acidemia, and hyperalaninemia are observed. In most cases, the disorder is lethal in infants.

Management

Evaluations Following Initial Diagnosis

When maple syrup urine disease (MSUD) is suspected during the diagnostic evaluation (i.e., due to elevated concentration of leucine, isoleucine, valine, and/or alloisoleucine), metabolic treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach to care with oversight and expertise from a specialized metabolic center. Consensus

nutritional guidelines have been published [Frazier et al 2014] (full text) and two peer-reviewed articles provide general guidelines about the comprehensive treatment and monitoring of MSUD: see Strauss et al [2010] (full text), Strauss et al [2020] (full text).

To establish the extent of disease and needs in an individual following initial diagnosis of MSUD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis of Maple Syrup Urine Disease

Evaluation/System	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietician [1]	• Transfer to specialist center w/experience in management of inherited metabolic diseases (strongly recommended). • Consider a short hospitalization at a center of expertise for inherited metabolic conditions to provide detailed education (natural history, maintenance & emergency treatment, prognosis & risks for acute encephalopathic crises to caregivers). • Determine whether patient has classic or intermediate MSUD through assessment of concentration ratios among the BCAAs & between leucine & other essential & nonessential amino acids. [2, 3, 4, 5]
Gastrointestinal/feeding	Swallow study as needed for symptomatic persons w/feeding difficulties &/or concern for aspiration
Developmental assessment	Consider referral to a developmental pediatrician.
Consultation w/neurologist	As needed for those w/neurologic findings
Consultation w/psychiatrist	For those w/signs of ADHD, anxiety, or depression
Consultation w/psychologist &/or social worker	To ensure understanding of the diagnosis & assess parental/patient's coping skills & resources
Consultation w/PT, OT, & speech therapist	As needed when developmental delays are present

ADHD = attention-deficit/hyperactivity disorder; BCAAs = branched-chain amino acids (leucine, isoleucine, and valine); OT = occupational therapist; PT = physical therapist

1. After a new diagnosis of MSUD in an infant or child, the closest hospital and local pediatrician should also be informed.

2. The following plasma concentration ratios are the most representative of amino acid regulation: leucine:isoleucine, leucine:valine, leucine:tyrosine, leucine:phenylalanine, leucine:glutamate, and leucine:alanine (mol:mol) [Mazariegos et al 2012].

3. In MSUD, plasma leucine concentration has the strongest reciprocal relationship to plasma alanine and glutamine concentrations (Spearman correlation coefficient -0.86 and -0.62, respectively; $p<0.0001$; see Figure 3) [Strauss et al 2010].

4. Severe branched-chain alpha-ketoacid dehydrogenase (BCKD) deficiency (classic MSUD) affects amino acid homeostasis at multiple levels and causes frequent and variable disturbances of plasma amino acid concentration ratios.

5. In milder intermediate forms of MSUD, plasma BCAAs may be chronically elevated while plasma amino acid concentration ratios tend to be preserved.

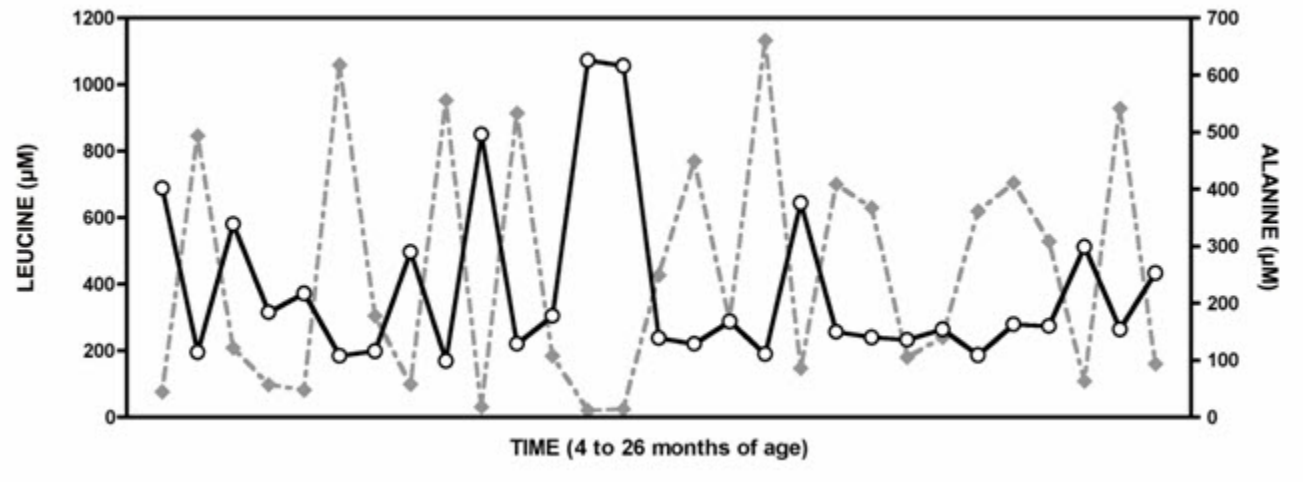

Figure 3. Plasma amino values between ages four and 26 months from a child with classic MSUD show a strong reciprocal relationship between leucine (gray diamonds) and alanine (white circles) (Spearman correlation coefficient = -0.86; p<0.0001).

Republished with permission from Strauss et al [2010]

Treatment of Manifestations

All children with MSUD and feeding difficulties require supervision of a specialist metabolic dietitian with experience in managing the diet of those with MSUD.

The main principles of treatment are age-appropriate tolerance of leucine, isoleucine, and valine, with stable plasma branched-chain amino acid (BCAA) concentrations and BCAA concentration ratios, while avoiding deficiencies of essential amino acids, fatty acids, and micronutrients (see Table 5).

Table 5. Routine Daily Treatment in Individuals with Maple Syrup Urine Disease

Age	Principle/ Manifestation	Treatment	Consideration/Other
Neonate/ Infant	Leucine restriction, titrated to leucine tolerance [1]	BCAA-free powder formula	Leucine tolerance for neonates is 65-85 mg/kg/day
		Natural protein as a source of essential & nonessential amino acids: 2-3 g/kg/day [2]	• Breast milk or regular infant formula can be used as a natural protein source. • For infants w/classic MSUD, breast milk should be expressed & quantified.
	Maintenance of adequate isoleucine & valine supplements	10 mg/mL solutions of isoleucine, valine, & leucine in distilled water	• Record of BCAA supplement intake maintained by parents • Dried blood spots by overnight mail for monitoring of amino acid concentrations (See Surveillance.) [3]

Table 5. continued from previous page.

Age	Principle/ Manifestation	Treatment	Consideration/Other
Child/ Adult	Leucine restriction, titrated to leucine tolerance [1]	Leucine tolerance: • Children: 20-40 mg/kg/day • Adults:10-15 mg/kg/day	• In persons w/classic MSUD (0%-2% enzyme activity) • See Figure 4. [4]
	Maintenance of adequate isoleucine & valine supplements	Maintain a plasma leucine-to-valine concentration ratio (mol:mol) of 0.5 or fewer and a leucine-to-isoleucine ratio of approximately 2.0	• Isoleucine supplements can periodically be suspended based on plasma amino acid monitoring, but continuous valine supplementation is recommended. [5] • Continuous valine fortification is directly related to long-term intellectual outcome. [2,6]
	Neuropsychiatric morbidity [7]	Standard psychostimulant & antidepressant medications as needed	
All ages	Normal age- & weight-adjusted energy intake	See Table 6 for patients from birth to age 4 yrs.	Information in Table 6 derived from Mennonite children birth to age 4 yrs w/classic MSUD
	Addressing ↑ energy/caloric demands	Fundoplication, gastrostomy, or jejunostomy to address feeding issues as needed in neurologically affected persons	• Adequate provision of information & education to parents, patients, & caregivers • For information on treatment during illness or acute decompensation, see Table 7 & Table 8.
	Gross motor delay	• PT • Aggressive rehab therapy	

BCAAs = branched-chain amino acids (leucine, isoleucine, and valine); PT = physical therapy

1. The dietary requirement for BCAAs varies as a function of age, growth rate, calorie intake, illness, and residual in vivo branched-chain alpha-ketoacid dehydrogenase (BCKD) enzyme activity.

2. For asymptomatic individuals; see Table 6 and Table 7 for acute management recommendations.

3. For rapidly growing infants, monitoring weekly or twice weekly is recommended.

4. Strauss et al [2010]

5. Valine has a low affinity for the blood-brain barrier LAT1 transporter, which makes it especially vulnerable to competitive inhibition by leucine.

6. Muelly et al [2013]

7. Which may include ADHD, depression, or anxiety

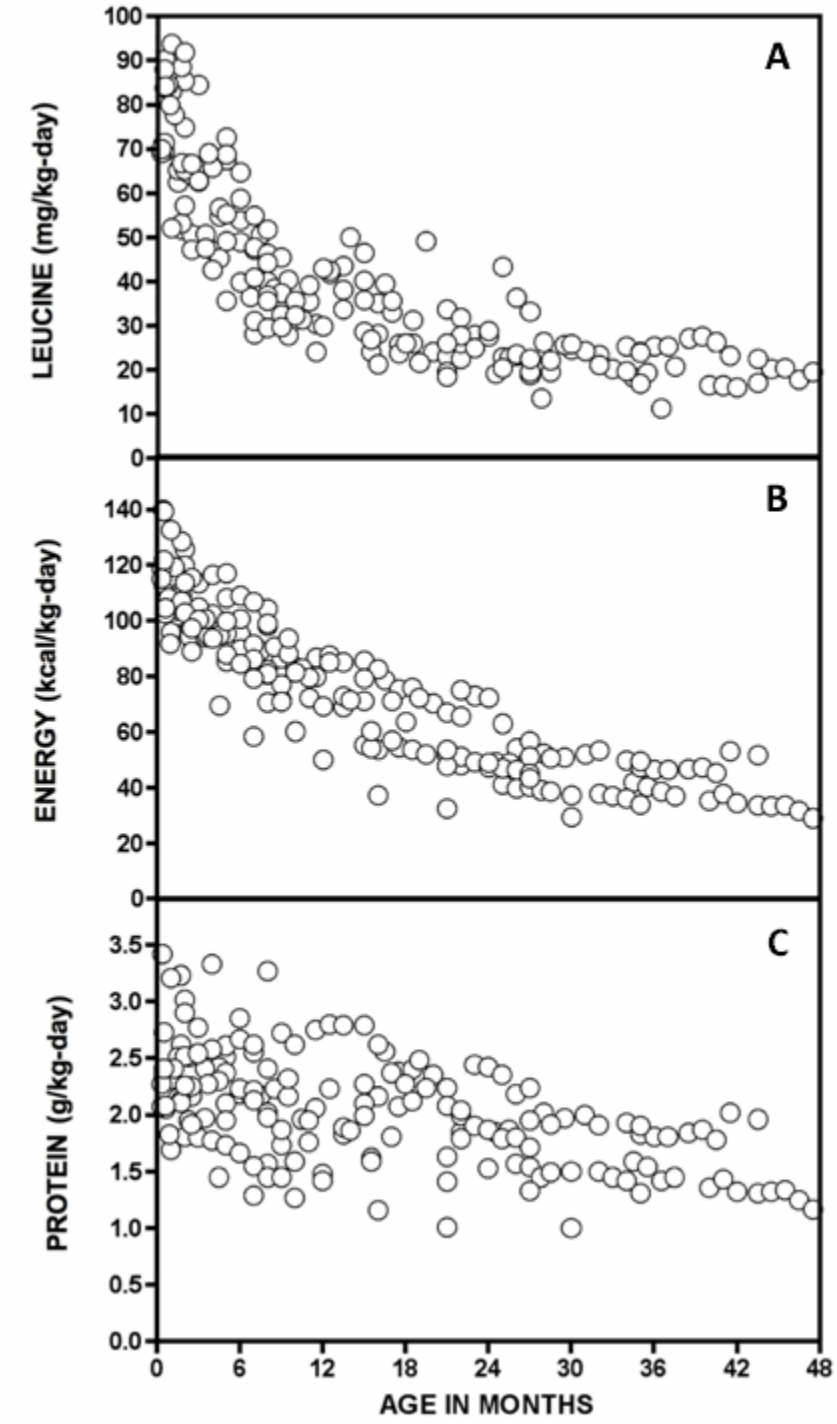

Figure 4. Leucine (A), energy (B), and total protein (C) intakes of 15 stable Mennonite infants with classic MSUD on dietary management

Republished with permission from Strauss et al [2010]

Table 6. Mean and 25th to 75th Percentile Range Nutrient Intakes (per kg-day) by Age Group

Nutrient	Age in Months (# of Persons)						
	0-2 (31)	3-5 (18)	6-8 (21)	9-12 (18)	13-18 (21)	19-24 (18)	25-36 (32)
	Mean Nutrient Intake per kg-day (25th to 75th %ile range)						
Leucine (mg)	72 (64-84)	58 (47-68)	44 (37-51)	35 (30-41)	33 (26-39)	27 (22-28)	21 (20-25)
Energy (kcal)	111 (103-119)	99 (94-107)	89 (82-99)	78 (71-87)	67 (55-77)	57 (49-71)	38 (39-51)
Total protein (g)	2.4 (2.1-2.6)	2.3 (1.9-2.6)	2.2 (1.8-2.5)	2.0 (1.5-2.5)	2.1 (1.8-2.4)	2 (1.7-2.3)	1.5 (1.5-2.9)
Leucine/ energy ratio (mg/ kcal)	0.65 (0.57-0.72)	0.58 (0.48-0.66)	0.50 (0.43-0.56)	0.46 (0.37-0.53)	0.50 (0.43-0.58)	0.48 (0.38-0.58)	0.54 (0.44-0.55)

Strauss et al [2010]; with permission from Elsevier
Data derived from Mennonite children from birth to age 4 years with classic MSUD

Mild illness. If an affected individual is clinically well despite an intercurrent infectious illness or febrile reaction to vaccinations, emergency outpatient management may be considered (see Table 7). If emergency outpatient treatment can be performed adequately and safely and if the child does not develop concerning symptoms during the illness, maintenance treatment and diet should be reintroduced stepwise over the next 48 (to 72) hours (see Table 5).

Table 7. Emergency Outpatient Treatment in Individuals with Maple Syrup Urine Disease

Manifestation/Concern	Treatment	Consideration/Other
Mildly increased catabolism [1]	↑ calorie intake & ↓ dietary leucine intake by using BCAA-free amino acid protein supplementation [2] orally or via tube feed.	• Trial of outpatient treatment at home for ≤12 hrs w/periodic measurement of urine BCKAs using DNPH strips • Reassessment (~ every 2 hrs) for clinical changes [3]
	↑ supplements of isoleucine & valine, 20-40 mg/kg/day each.	Measurement of plasma or whole-blood amino acids every 24-48 hrs
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperatures rises >38.5°C	
Occasional vomiting	Antiemetics [4]	

BCAA = branched-chain amino acid; BCKAs = branched-chain alpha-ketoacids; DNPH = dinitrophenylhydrazine
1. Fever <38.5°C (101°F), enteral or gastrostomy tube feeding tolerated without recurrent vomiting or diarrhea, and absence of neurologic symptoms (altered consciousness, irritability, hypotonia)
2. High-calorie BCAA-free "sick day" formulas
3. Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features discussed with the designated center of expertise for inherited metabolic diseases
4. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Acute decompensation. Dietary indiscretion causes plasma BCAAs to increase but only rarely results in acute decompensation and encephalopathy. In contrast, infections and injuries trigger a large endogenous mobilization of muscle protein and can precipitate metabolic crisis and hospitalization.

Acute manifestations (e.g., lethargy, encephalopathy, seizures, or progressive coma) should be managed symptomatically and with generous caloric support in a hospital setting (see Table 8). Correction of metabolic decompensation is predicated on treating the underlying cause of the decompensation and establishing net protein accretion.

Table 8. Acute Inpatient Treatment in Individuals with Maple Syrup Urine Disease

Principle Goal/ Manifestation	Treatment/Monitoring during Acute Treatment	Consideration/Other
To correct metabolic derangements due to MSUD [1]		
↓ plasma leucine concentration by 500-1,000 µmol/L per 24 hrs.	Provide 1.5x-3x EER as dextrose (50%-70%) & lipid (30%-50%).	When central access allows, use 25% dextrose solutions to minimize complications of hypervolemia.
	Continuous insulin infusion: 0.02-0.15 U/kg/hr	Titrate insulin infusion to maintain blood glucose 100-160 mg/dL.
	Total protein intake (enteral + parenteral): 2.0-3.5 g/kg/day as BCAA-free amino acids	• Hospitals admitting patients w/MSUD encephalopathy should have an established mechanism for procuring MSUD parenteral amino acid solutions devoid of BCAAs. [2] • For patients of any age who can tolerate enteral feeding (even if intubated), continuous nasogastric delivery (30-60 mL/hr) of a BCAA-free MSUD formula (0.7-1.2 kcal/mL) supplemented w/1% liquid solutions of isoleucine & valine can meet protein goals while providing addl calories. [3]
	Isoleucine & valine supplements (enteral + parenteral): 20-120 mg/kg/day each; titrate to plasma concentrations of 400-800 µmol/L	For parenteral administration, isoleucine & valine are each prepared as separate 1% solutions in normal saline.
	Consider renal replacement therapies in clinical settings w/appropriate resources & expertise [4]	• Peritoneal dialysis & venovenous hemofiltration are less effective & more dangerous than short courses of continuous hemodialysis. [5] • When hemodialysis is used to treat MSUD it must be coupled w/effective nutritional management to constrain catabolic response & prevent recurrent clinical intoxication. [6, 7]
To prevent iatrogenic electrolyte abnormalities, [8, 9] which can → cerebral edema & intracranial hypertension		
Maintain serum osmolality in normal reference range (275-300 mOsm/kg H_2O).	Establish euvolemia using *isotonic* sodium chloride solutions.	
	Measure serum osmolality & electrolytes every 6-12 hours.	Prevent serum osmolality from decreasing >5 mOsm/kg H_2O per day (0.20 mOsm/kg H_2O per hr).

Table 8. continued from previous page.

Principle Goal/ Manifestation	Treatment/Monitoring during Acute Treatment	Consideration/Other
Monitor for other laboratory abnormalities.	Serum (&/or point-of-care) glucose every 4-6 hrs	
	Plasma amino acids, serum phosphorus, & magnesium every 12-24 hrs	Hospitals admitting patients w/MSUD encephalopathy should be able to perform plasma amino acid testing around the clock.
	Serum lipase, amylase, & transaminases every 24-48 hours	
Manage cerebral edema.	Monitor for signs of intracranial hypertension & impending brain herniation.	Mgmt in an intensive care setting w/consultation by neurologist &/or neurointensivist is recommended
	For obtunded patients w/cerebral edema, consider endotracheal intubation for airway protection & neurosurgical consultation to consider measures incl, e.g., intracranial pressure monitoring & active CSF drainage.	Acute neuroimaging may be indicated in some circumstances. [10]
	Treat symptomatic hypo-osmolality or worsening signs of intracranial hypertension using the following agents alone or in sequence: mannitol 0.5-1 mg/kg per dose; hypertonic (3%) saline 2-3 mEq/kg per dose; furosemide 0.5-1.0 mg/kg per dose	In those w/moderate-to-severe encephalopathy, consider administration of hypertonic (3%) saline drip: 5-15 mEq/kg per day sodium chloride titrated to serum osmolality 290-300 mOsm/kg H_2O, serum sodium 138-145 mEq/L, & serum osmolality change <0.2 mOsm/kg H_2O per hr (5 mOsm/kg H_2O per day)
General measures		
Identify & treat precipitating catabolic stress (e.g., infection, dehydration, trauma).	Low clinical threshold for empiric administration of antibiotics when signs of infection are present	• Superficial & invasive *Candida* infections are common. • Persons w/MSUD are vulnerable to bacterial or fungal infection from central venous catheters
	Schedule antipyretics (e.g., acetaminophen, ibuprofen, ketorolac) to control fever	Ketorolac contraindicated in those who are dehydrated, known to have kidney disease, or taking other medications that affect renal perfusion
	Antiemetics to control nausea & vomiting	Consider scheduled intravenous ondansetron 0.15 mg/kg per dose every 6-8 hours
	Limit use of glucocorticoids & vasoactive catecholaminergic agents	
Other complications		
Acute pancreatitis [11]	• Stop all enteral feeding & measure serum concentrations of lipase & amylase. [12] • Supportive treatment w/BCAA-free parenteral nutrition solutions	

Table 8. continued from previous page.

Principle Goal/ Manifestation	Treatment/Monitoring during Acute Treatment	Consideration/Other
Dystonia assoc w/metabolic crisis [13]	Enteral tyrosine at 100-400 mg/kg/day	Tyrosine dissolves poorly in aqueous solution, so enteral administration is typically required

BCAAs = branch-chain amino acids (leucine, isoleucine, and valine); EER = estimated energy expenditure

1. Establish central venous access; where regional expertise allows, the authors recommend placement of a peripheral intravenous central catheter (PICC) or other form of central line for treatment of metabolic intoxication.

2. Parenteral MSUD amino acid solutions are the preferred protein source for individuals with MSUD who have severe metabolic encephalopathy; however, such parenteral solutions are available from a very limited number of specialty pharmacies and often prove difficult to procure in a timely manner.

3. Nyhan et al [1998], Morton et al [2002]

4. Nutritional therapy alone can effectively reduce even extremely elevated plasma concentrations of leucine in persons with MSUD of any age and under a wide variety of clinical circumstances [Morton et al 2002, Strauss & Morton 2003]. However, numerous publications have shown that renal replacement methods can achieve rapid corrections of branched-chain amino acids (BCAAs) and branched-chain alpha-ketoacids (BCKAs) during the acute phase of MSUD crisis [Jouvet et al 1997, Schaefer et al 1999, Yoshino et al 1999, Jouvet et al 2001, Puliyanda et al 2002].

5. Schaefer et al [1999]

6. A combined approach to therapy, using hemodialysis with simultaneous anabolic nutritional therapy was shown to be highly effective in one neonate with classic MSUD [Puliyanda et al 2002].

7. Dialysis without simultaneous management of the underlying disturbance of protein turnover is analogous to treating diabetic ketoacidosis with invasive removal of glucose and ketones rather than insulin infusion. In both conditions, effective treatment depends not only on lowering concentrations of pathologic metabolites, but also on controlling the underlying metabolic derangement (in this case ongoing protein degradation due to catabolism).

8. Most commonly associated with high intravenous fluid, glucose, and insulin infusions.

9. The most commonly encountered biochemical complications of treatment are hyperglycemia, hypoglyemia, hyponatremia, hypokalemia, and hypophosphatemia.

10. During episodes of acute encephalopathy, individuals with MSUD are typically too unstable for magnetic resonance imaging. Cranial CT scan is used to evaluate for major indices of cerebral edema, such as decreased volume of cerebral ventricles and basal fluid spaces, or reduced gray-white discrimination (see Figure 2). New scanners are designed for portable use in the intensive care setting.

11. Signs and symptoms typically include epigastric or mid-back pain, anorexia, and/or vomiting, developing in two to three days into treatment of a metabolic decompensation.

12. Kahler et al [1994]

13. During acute metabolic crisis, newborns, infants, and children with MSUD can develop acute focal or generalized dystonic posturing attributed to an increased plasma leucine:tyrosine concentration ratio, restricted brain tyrosine uptake, and reduced cerebral dopamine synthesis [Morton et al 2002, Zinnanti et al 2009].

Prevention of Primary Manifestations

Table 9. Prevention of Primary Manifestations in Individuals with Maple Syrup Urine Disease

Manifestation/ Situation	Prevention	Considerations/Other
Metabolic cure	Orthotopic liver transplantation	• Effective for classic MSUD, w/removal of dietary restrictions & complete protection from decompensations during illness [1] • Post transplantation, plasma leucine, isoleucine, & valine concentrations typically normalize w/in 6 hrs & chronically remain ~2x the reference mean on an unrestricted diet. • Disease-free survival & graft survival are high, 100% in a series of 93 patients transplanted at University Pittsburgh Medical Center between 2003 & 2019. [2] • Risks assoc w/surgery & immunosuppression are similar to those in other pediatric liver transplant populations & may incl EBV-assoc post-transplantation lymphoproliferative disease. • Liver transplantation does not reverse cognitive disability or psychiatric illness in patients w/MSUD but may arrest progression of neurocognitive impairment & prevent life-threatening cerebral edema assoc w/metabolic crisis. [3, 4]
Neuropsychiatric morbidity	Strict & consistent metabolic control [4]	
Potential thiamine responsiveness [5]	Consider a 4-wk trial of enteral thiamine (50-100 mg/day, divided 2x/day)	Significant changes in dietary therapy (e.g., BCAA or calorie intake) during treatment period confounds interpretation of a specific thiamine effect.

BCAA = branched-chain amino acid; EBV = Epstein-Barr virus
1. Wendel et al [1999], Bodner-Leidecker et al [2000], Strauss et al [2006], Mazariegos et al [2012]
2. Strauss et al [2020]
3. Shellmer et al [2011], Mazariegos et al [2012]
4. Muelly et al [2013]
5. The existence of "thiamine-responsive" branched-chain alpha-ketoacid dehydrogenase (BCKD) mutants is controversial.

Prevention of Secondary Complications

Any trauma care or surgical procedures should be approached in consultation with a metabolic specialist.

Surveillance

Table 10. Recommended Surveillance for Individuals with Maple Syrup Urine Disease

Manifestation	Evaluation	Frequency/Comment
Control of amino acid & other nutrient levels [1]	Full amino acid profile (either from plasma or filter paper)	• For rapidly growing infants, monitoring 1x or 2x/wk • Weekly in children, adolescents, & adults [2, 3]
	Measurement of calcium, magnesium, zinc, folate, selenium & omega-3 essential fatty acid	As indicated based on clinical signs of deficiency
	Visit w/metabolic specialist	At least monthly in infancy

Table 10. continued from previous page.

Manifestation	Evaluation	Frequency/Comment
Delayed acquisition of developmental milestones	Monitor developmental milestones [4,5]	At each visit or as needed

1. See **Goals of laboratory monitoring** (following) for target concentrations for various amino acids and other nutrients.
2. The frequency of amino acid monitoring varies by age, metabolic stability, adherence, and regional clinical practice.
3. The frequency of amino acid monitoring correlates directly with metabolic control [Strauss et al 2020] and long-term measures of intelligence [Muelly et al 2013].
4. The Denver Developmental Screening Test II or a comparable tool is useful for monitoring development of infants and young children with MSUD.
5. School-age children, adolescents, and adults should have neurocognitive testing if indicated by school performance or behavior problems [Shellmer et al 2011, Muelly et al 2013].

Goals of laboratory monitoring

- Plasma leucine concentration: 150-300 µmol/L with an age-appropriate intake
- Plasma isoleucine concentration approximately equal to plasma leucine concentration
- Plasma valine concentration at least twofold plasma leucine concentration
- Indices of calcium, magnesium, zinc, folate, selenium, and omega-3 essential fatty acid sufficiency

Evaluation of Relatives at Risk

Early diagnosis of at-risk sibs of an affected individual may allow asymptomatic infants to be managed out of the hospital by experienced providers.

Newborn at-risk sibs who have not undergone prenatal testing can be tested in one of two ways:

- Plasma amino acid analysis of a sample obtained at approximately 24 hours of life. In some laboratories, samples obtained earlier can yield false negative results.
- If the pathogenic variants have been identified in the family, a cord blood sample can be used for molecular genetic testing.

Before confirmatory molecular testing is complete, at-risk neonates can be managed with an MSUD prescription diet if serial plasma amino acid profiles provide evidence of MSUD.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

With the advent of newborn screening and preventive care, more women with MSUD are surviving to child-bearing age. Successful delivery of a healthy baby is possible for women with classic MSUD [Van Calcar et al 1992, Grünewald et al 1998]. Two women who had biallelic pathogenic *BCKDHA* variants became pregnant following liver transplantation. Each delivered a healthy baby after remaining on immunosuppressant medication (sirolimus) but observing no special dietary restrictions during pregnancy [Strauss et al 2020].

Elevated maternal leucine plasma concentration, like elevated maternal phenylalanine plasma concentration, is likely teratogenic. If a woman with MSUD is planning a pregnancy, metabolic control should be maintained in a rigorous fashion preceding and throughout gestation. Keeping the maternal plasma levels of the branched-chain amino acids between 100 and 300 µmol/L is compatible with delivery of a normal infant [Grünewald et al 1998].

During the development of the placenta and fetus, maternal BCAA and protein requirements increase, and frequent monitoring of plasma amino acid concentrations and fetal growth may be necessary to avoid essential amino acid deficiencies [Grünewald et al 1998].

The postpartum period is dangerous for the affected mother. Catabolic stress of labor, involutional changes of the uterus, and internal sequestration of blood are potential sources of metabolic decompensation [Chuang & Shih 2001]. Appropriate monitoring at a metabolic referral center is advised at the time of delivery.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Maple syrup urine disease (MSUD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *BCKDHA*, *BCKDHB*, or *DBT* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with maple syrup urine disease are obligate heterozygotes (carriers) for a *BCKDHA*, *BCKDHB*, or *DBT* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *BCKDHA*, *BCKDHB*, or *DBT* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *BCKDHA*, *BCKDHB*, or *DBT* pathogenic variants in the family.

Biochemical testing. Quantitative plasma amino acids and fibroblast enzymatic analyses are not indicated for detection of heterozygotes.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *BCKDHA*, *BCKDHB*, or *DBT* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk for MSUD are possible.

Biochemical testing. If only one or neither pathogenic variant is known within a family, branched-chain alpha-ketoacid dehydrogenase (BCKD) enzyme activity can be measured from cultured amniocytes obtained by amniocentesis (usually performed at ~15-18 weeks' gestation) or chorionic villus cells obtained by chorionic villus sampling (usually performed at ~10-12 weeks' gestation).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**

  TEMPLE (Tools Enabling Metabolic Parents LEarning)

  United Kingdom

  MSUD

- **Medical Home Portal**

  Maple Syrup Urine Disease (MSUD)

- **MSUD Family Support Group**

  The MSUD Family Support Group is a non-profit 501 (c)(3) organization for those with MSUD and their families and includes health-care professionals and others interested in MSUD.

  Phone: 740-972-5619

  Email: sandybulcher@gmail.com

  www.msud-support.org

- **National Library of Medicine Genetics Home Reference**

  Maple syrup urine disease

- **NCBI Genes and Disease**
  Maple syrup urine disease
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Maple Syrup Urine Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BCKDHA	19q13.2	2-oxoisovalerate dehydrogenase subunit alpha, mitochondrial	BCKDHA database	BCKDHA	BCKDHA
BCKDHB	6q14.1	2-oxoisovalerate dehydrogenase subunit beta, mitochondrial	BCKDHB database	BCKDHB	BCKDHB
DBT	1p21.2	Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex, mitochondrial	DBT database	DBT	DBT

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Maple Syrup Urine Disease (View All in OMIM)

248600	MAPLE SYRUP URINE DISEASE, TYPE IA; MSUD1A
248610	DIHYDROLIPOAMIDE BRANCHED-CHAIN TRANSACYLASE; DBT
248611	BRANCHED-CHAIN KETO ACID DEHYDROGENASE E1, BETA POLYPEPTIDE; BCKDHB

Table B. continued from previous page.

608348	BRANCHED-CHAIN KETO ACID DEHYDROGENASE E1, ALPHA POLYPEPTIDE; BCKDHA
620698	MAPLE SYRUP URINE DISEASE, TYPE IB; MSUD1B
620699	MAPLE SYRUP URINE DISEASE, TYPE II; MSUD2

Molecular Pathogenesis

Maple syrup urine disease (MSUD) is caused by decreased activity of human branched-chain alpha-ketoacid dehydrogenase complex (BCKD), a multi-enzyme complex found in the mitochondria. It catalyzes the oxidative decarboxylation of the branched-chain ketoacids (alpha-ketoisocaproate, alpha-keto-beta-methyl valerate, and alpha-ketoisovalerate) in the second step in the degradative pathway of the branched-chain amino acids (BCAAs; leucine, isoleucine, and valine).

BCKD has four subunit components (E1a, E1b, E2, and E3). Biallelic pathogenic variants in one of the four unlinked genes encoding any subunit can result in decreased activity of the enzyme complex and the accumulation of BCAAs and corresponding branched-chain alpha-ketoacids (BCKAs) in tissues and plasma [Nellis et al 2003, Chuang et al 2004].

Biochemical derangements caused by pathogenic variants in the genes encoding BCKA decarboxylase (E1) alpha subunit (MSUD type 1A), BCKA decarboxylase (E1) beta subunit (MSUD type 1B), and dihydrolipoyl transacylase (E2) subunit (MSUD type 2) are indistinguishable biochemically.

Note: The E3 subunit (lipoamide dehydrogenase encoded by *DLD*) of BCKD is shared with the pyruvate and alpha-ketoglutarate dehydrogenase complexes, and MSUD type 3 is characterized by increased urinary excretion of BCKAs and alpha-ketoglutarate accompanied by elevated plasma concentrations of lactate, pyruvate, and alanine (see Table 2). However, the clinical phenotype of E3 subunit deficiency differs considerably from the classic and intermediate forms of MSUD and is not discussed further in this *GeneReview*.

The BCKD complex consists of three catalytic components:

- The E1 decarboxylase, which is a heterotetramer of alpha and beta subunits (alpha2, beta2)
- The E2 transacylase, which is a homo-24-mer
- The E3 dehydrogenase, which is a homodimer

The complete functional BCKD complex contains a cubic E2 core surrounded by the following:

- Twelve E1 components
- Six E3 components
- A single kinase

BCKD colocalizes with BCAA transaminases in mitochondria of diverse tissues and is regulated by a kinase-phosphatase pair. In humans, skeletal muscle is the major site for both transamination and oxidation of BCAAs. The liver and kidney each mediate an estimated 10%-15% of whole-body BCAA transamination-oxidation [Suryawan et al 1998]. BCKD is expressed in the brain, where BCAA transamination-oxidation may contribute to cerebral glutamate and GABA production [Yudkoff et al 2005].

Mechanism of disease causation. MSUD is a recessive disorder caused by biallelic pathogenic variants in *BCKDHA*, *BCKDHB*, or *DBT* that result in decreased function or loss of function.

Table 11. Maple Syrup Urine Disease: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
BCKDHA	Pathogenic missense variant(s) reported in 3'UTR [2]
DBT	Pathogenic missense variant(s) reported in 3'UTR [2]; a higher-than-expected percentage of *DBT* pathogenic variants are deletions (both large and small) [3]

1. Genes from Table 1 in alphabetic order
2. Deletions may be mediated by nonallelic homologous recombination between repetitive elements. However, these elements are not more abundant in *DBT* and there is, to date, no adequate explanation for the increased frequency of deletions in *DBT*.
3. As described in the Human Gene Mutation Database [Stenson et al 2020]

Table 12. Maple Syrup Urine Disease: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [2])	Comment
BCKDHA	NM_000709.2 NP_000700.1	c.1312T>A	p.Tyr438Asn (Tyr393Asn)	Founder variant in Swiss Mennonites [Fisher et al 1991, Puffenberger 2003] (See Prevalence.)
	NM_000709.2	c.288+9C>T	--	Assoc w/variant MSUD [Fernández-Guerra et al 2010]
	NM_000709.2 NP_000700.1	c.919G>A	p.Arg297His	Assoc w/variant MSUD [Flaschker et al 2007]
		c.982G>A	p.Ala328Thr	Assoc w/variant MSUD [Flaschker et al 2007]
BCKDHB	NM_183050.2 NP_898871.1	c.548G>C	p.Arg183Pro	Founder variant in Ashkenazi Jews [Edelmann et al 2001]
		c.598C>G	p.Pro200Ala	Assoc w/variant MSUD [Flaschker et al 2007]
		c.767A>G	p.Tyr256Cys	Assoc w/intermittent MSUD [Guo et al 2015]
		c.832G>A	p.Gly278Ser	Assoc w/intermittent MSUD [Edelmann et al 2001, Henneke et al 2003, Flaschker et al 2007, Puckett et al 2010, Boros et al 2017, Szuch & Auriemma 2018]

Table 12. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [2])	Comment
DBT	NM_001918.4 NP_001909.3	c.747_773del	p.Gly249_Lys257del	Assoc w/intermittent MSUD [Flaschker et al 2007]
		c.827T>G	p.Phe276Cys	Assoc w/intermittent MSUD [Chuang et al 1991]
		c.871C>G	p.Arg291Gly	Assoc w/intermittent MSUD [Chuang et al 1991]
		c.901C>T	p.Arg301Cys	Assoc w/intermittent MSUD [Brodtkorb et al 2010]
		c.920T>C	p.Phe307Ser	Assoc w/variant MSUD [Flaschker et al 2007]
		c.1196C>G	p.Ser399Cys	Founder variant in the Malay population [Ali & Ngu 2018]
		c.1430T>G	p.Met477Arg	Assoc w/intermittent MSUD [Puckett et al 2010]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order
2. Variant designation that does not conform to current naming conventions

Chapter Notes

Author History

D Holmes Morton, MD; Clinic for Special Children (2006-2020)
Erik G Puffenberger, PhD (2006-present)
Kevin A Strauss, MD (2006-present)
Vincent J Carson, MD (2020-present)

Revision History

- 23 April 2020 (ma) Comprehensive update posted live
- 9 May 2013 (me) Comprehensive update posted live
- 15 December 2009 (me) Comprehensive update posted live
- 30 January 2006 (me) Review posted live
- 22 November 2004 (ep) Original submission

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