6 Disorders of Leucine Metabolism

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6.1 Introduction

Of the disorders of leucine metabolism, only maple syrup urine disease (MSUD) is associated with elevated body fluid levels of the branched-chain amino acids (BCAA), namely leucine, isoleucine, and valine. Due to irreversible steps early in the metabolism of the BCAA, elevated levels of these amino acids do not occur in those disorders that result from blocks in the pathways distal to the site of MSUD. Rather, the disorders are associated with organic acidemias/acidurias.

Severe forms of the disorders of leucine metabolism present as acute, overwhelming metabolic illness in the neonatal period, often during the 1st week of life. Other milder or variant forms may be episodic and might not become symptomatic until late childhood or even adult life. Also, some patients are asymptomatic and identified only through family studies or by newborn screening.

Maple syrup urine disease results from deficient activity of the branched-chain α-ketoacid dehydrogenase complex (BCKDC). During episodes of metabolic decompensation, the BCAA and their corresponding branched-chain α-ketoacids (BCKA) accumulate. At such times, affected patients have the odor of maple syrup in body fluids and cerumen from 2-oxo-3-methylvalerate, after which the disorder is named. The BCKDC consists of three catalytic components (E1, E2, and E3) encoded by four different genetic loci. The E1 component is a thiamine pyrophosphate-dependent decarboxylase comprised of two subunits, α and β, which are encoded by two separate loci. The E2 component is a dihydrolipoyl acyltransferase and the E3 component a lipoamide dehydrogenase. A regulatory BCKDC-specific kinase and phosphatase are also involved but not yet fully characterized. Mutations in all four of the catalytic loci have been associated with clinical disease.

Five *clinical forms* of MSUD exist, which are differentiated by the amount of residual enzymatic activity, age and severity of onset, and responsiveness to thiamine, a cofactor for the BCKDC. *Classic MSUD* patients present with poor feeding, lethargy, abnormal movements, and a progressive encephalopathy during the 1st week of life. Most patients have less than 2% of normal BCKDC specific activity; they are not responsive to thiamine administration.

Intermediate MSUD has similar symptoms, but with a later, variable age of onset. Patients have between 3 and 30% of normal residual specific activity of the BCKDC and they are not responsive to thiamine. *Intermittent MSUD* is characterized by episodes of ataxia and ketoacidosis that are associated with intercurrent illnesses or increased protein intake. Affected patients have between 5 and 20% of normal residual specific activity of the BCKDC and are not responsive to thiamine. Patients with *thiamine-responsive MSUD* have between 2 and 40% of normal residual specific activity of the BCKDC and show varying degrees of correction of their metabolic abnormalities in response to pharmacologic doses of thiamine. *Deficiency of the E3 component* results in decreased activity of the BCKDC (0–25% of normal) along with reduced activity of the pyruvate dehydrogenase complex and the 2-oxoglutarate dehydrogenase complex, because the E3 component is common to all three mitochondrial complexes. These patients have a combination of symptoms and biochemical findings for all three of the individual deficiencies and present during infancy with acidosis and a progressive encephalopathy. Although all three BCAA are elevated in body fluids, the pathophysiology of all forms of MSUD is thought to be related to the elevated levels of leucine.

With advances in the molecular pathology of MSUD, a certain degree of molecular genotype-clinical phenotype correlation has emerged. Patients with E1α and E2 mutations have varying clinical presentations (classic, intermittent, intermediate), depending upon the specific mutation involved. To date, all reported patients with E1β mutations have had the severe, classic clinical form of the disorder. All reported thiamine-responsive patients have had E2 mutations. The most frequent mutation, the E1α mutation Y393N, is associated with a severe classic presentation and found not only in the Mennonites, among whom it is common, but also in the general population in North America. Another common E1α mutation, G241R, is associated with intermediate clinical disease in the Hispanic-Mexican population. In that specific mutations have been shown to be associated with a certain type of clinical disease, determining the exact mutation involved through mutational analysis will help guide clinical management for the individual patient, especially in regard to the need for thiamine supplementation and the degree of restriction of dietary natural protein necessary to control the disorder (Chuang and Shih 2001; Morton et al. 2002).

Classic isovaleric acidemia (IVA) results from deficient activity of isovaleryl-CoA dehydrogenase and patients present with acute, neonatal metabolic disease or with chronic, intermittent episodes during the 1st years of life. Affected patients have the odor of "sweaty feet." In addition to marked ketoacidosis, they may have bone marrow suppression and significant secondary hyperammonemia. Reduced activity of isovaleryl-CoA dehydrogenase also occurs as part of multiple acyl-CoA dehydrogenase deficiency, which is discussed with the disorders of mitochondrial fatty acid oxidation (Sweetman and Williams 2001; Ogier de Baulny and Saudubray 2002).

Patients with *isolated 3-methylcrotonyl-CoA carboxylase* (3MCCC) *deficiency* often have acute episodes of vomiting, hypotonia, seizures, and coma, accompanied by an "acid" odor. Mutations in either of the loci that encode for the two subunits of the enzyme are clinically indistinguishable. Both mild and severe clinical forms of the disorder have been reported. Still others, detected through newborn screening or family studies, are asymptomatic. Many of the patients detected through newborn screening have had transient elevations of abnormal metabolites suggestive of 3MCCC deficiency. Others do not have the disorder, but have abnormal metabolites from affected mothers with mild forms of the disorder. It is important that the appropriate testing (urine organic acid analysis, enzymatic assay) be done on such infants, and their mothers if indicated, to confirm whether they have the disease prior to placing the infant on a protein-restricted diet (Gibson et al. 1998). 3MCCC deficiency also occurs as part of multiple CoA carboxylase deficiency, which is discussed with the disorders of biotin metabolism in Chap. 7, Disorders of Valine-Isoleucine Metabolism.

Patients with the four types of *3-methylglutaconic aciduria* have varying symptoms. Patients with type I, associated with reduced activity of 3-methylglutaconyl-CoA hydratase, present with a wide spectrum of clinical symptoms, from none to severe neurological impairment or acute acidosis (Sweetman and Williams 2001). The basic enzymatic defect and etiology for the presumed secondary 3-methylglutaconic aciduria in types II, III, and IV is unknown. Type II, also known as Barth syndrome, is an X-linked disorder characterized by skeletal myopathy, dilated cardiomyopathy, short stature, recurrent neutropenia, and mild hypocholesterolemia. Barth syndrome has been associated with the *TAZ* genetic locus at chromosome Xq28, which encodes a protein of unknown function, tafazzin, that is highly expressed in cardiac and skeletal muscle (Barth et al. 1999; Ostman-Smith et al. 1994). Type III, known as Costeff optic atrophy syndrome, presents with a movement disorder in addition to optic degeneration. The syndrome has been linked to the genetic loci OPA3 at chromosome 19q13.2-q13.3 (Costeff et al. 1989; Elpeleg et al. 1994). Type IV, or the unclassified form, is often seen with neurological, peripheral organ, and other metabolic disturbances. Because types II, III, and IV do not involve defects in the leucine pathway, treatment for patients with these forms of the disorder will not be discussed in this chapter.

Patients with *3-hydroxy-3-methylglutaric acidemia* (HMG-CoA lyase deficiency) most often present with neonatal hypoketotic hypoglycemia and acidosis. Milder forms of the disorder also have been reported (Dasouki et al. 1987; Gibson et al. 1988).

The mainstay of treatment with all the disorders is to limit leucine intake while preventing catabolism. With severe forms of the disorders, special medical foods, devoid of leucine or the BCAA, are needed to allow for adequate caloric, protein, and other nutrient intake. Milder forms may only require a reduced natural protein intake. The amount of leucine or BCAA needed for growth and tissue repair is supplied from measured amounts of standard infant formula

in young children and whole cow's milk and table foods in older patients. The amount of natural whole protein tolerated is determined by monitoring parameters such as growth, control of acidosis, blood quantitative amino acid levels, and testing for body protein stores. Protein intake should be adequate to promote normal growth without contributing to uncontrolled disease. The least restrictive dietary approach should be taken in order to avoid overtreatment and BCAA deficiency.

Patients with the severe forms of MSUD (classic, intermediate forms) have a very low tolerance of natural dietary leucine. To control the disorder yet have adequate nutrition, special medical foods devoid of the BCAA are needed, usually for the life of the affected individual (Acosta and Yannicelli 2001; Chuang and Shih 2001; Morton et al. 2002; Strauss and Morton 2003) (Table 6.1).

Table 6.1. Nutritional treatment for severe forms of maple syrup urine disease[a]

Age	Protein requirement[b] (g/kg per day)	Leucine tolerance[c] (mg/kg per day)	Isoleucine intake (mg/kg per day)	Valine intake (mg/kg per day)	Energy requirement[c] (kcal/kg per day)
Neonates	2.5–3.0	50–90	20–50	30–60	120–145
Infants	2.0–3.0	40–80	20–50	30–60	115–145
Young children	1.5–2.0	20–40	5–15	10–30	60–80
Older children and adults	1.0–1.2	5–15	5–15	10–30	40–60

[a] Modified from Strauss and Morton 2003 and Acosta and Yannicelli 2001. These recommendations are only a guide and should be individualized for each patient, based on the severity of their disorder and blood quantitative amino acid levels
[b] Includes protein intake from special medical foods devoid of BCAA plus that from natural whole protein sources
[c] Leucine (milligrams) to kilocalorie ratio of 0.5–0.8 for neonates and infants; ratio of 0.25–0.30 in children and older. Lipids should comprise 40–50% of total calories. Formula concentrations over 0.8 kcal/ml may result in loose stools, diarrhea, and dehydration

Milder forms of MSUD (intermittent, thiamine-responsive) often respond to a lowered natural protein intake of 1.5–2.0 g/kg per day in young infants or 0.6–1.5 g/kg per day in older children and adults. Additional nonprotein calories may be supplied with otherwise complete, protein-free, special medical foods to meet energy requirements. Special low-protein food products, i. e., bread, pasta, cereals, are also available.

Leucine competes with other large, neutral amino acids, including valine and isoleucine, for an L-amino acid transporter-1 (LAT1) that is responsible for carrying the amino acids across cell membranes. By supplying the other amino acids involved in increased concentration, this not only corrects any intracellular deficit of the other amino acids that may have occurred from the elevated leucine levels, but also decreases leucine uptake. Supplements of isoleucine and valine are routinely given with MSUD for this reason, as well as to maintain target blood levels. Additional supplements of glutamine, alanine,

and occasionally of tyrosine, are used. This approach is especially useful in controlling leucine levels in severe forms of MSUD (Strauss and Morton 2003).

In the disorders of leucine metabolism other than MSUD, the toxic metabolites are organic acids and not the precursor amino acid leucine. Treatment is aimed at reducing leucine intake and thereby reducing the organic acid formation, while preventing catabolism. Although control of leucine intake is needed, strict control of blood leucine levels is not as critical as in MSUD. Rather, it is important that overtreatment does not occur and leucine deficiency not develop. For this reason, treatment should employ the least restrictive dietary approach needed for metabolic control (Ogier de Baulny and Saudebray 2002; Sweetman and Williams 2001; Thompson et al. 1990).

With the severe, early onset forms of IVA, 3MCCC deficiency, 3MG1, and HMGCL deficiency, special medical foods devoid of leucine may be needed in order to control the disorder and prevent toxic organic acid accumulation, especially during the neonatal period and early infancy. Many patients with these disorders, however, even some with early onset forms, do not require this restrictive a diet and will respond to a reduction in the intake of natural protein without the need for the special medical food. Two approaches to the initial nutritional management may be taken. Firstly, a lowered natural protein diet may be started, along with supplements of otherwise complete, protein-free, special medical food to meet energy requirements. If the protein requirement for growth cannot be tolerated without organic acid accumulation, then special medical food devoid of leucine is added until growth is established and the disorder controlled. Alternatively, a diet employing special medical foods devoid of leucine may be given initially. As natural protein intake is added and advanced, the growth pattern and degree of control of the disorder are monitored. Assessment of the clinical course and the amount and source of protein intake (natural vs special medical food) are helpful in determining whether the special medical food devoid of leucine needs to be continued or not. As occurs with chronic diseases, including other inborn errors (i. e., PKU, homocystinuria), many of the patients self-discontinue treatment, including the use of special medical foods, during late childhood or early adolescence for various reasons, e. g., odor, taste. Protein-free, otherwise complete special medical foods and special low-protein food products are often needed to supply the caloric requirement of such individuals (Table 6.2).

Table 6.2. Nutritional treatment for severe forms of isovaleric acidemia[a]

Age	Protein requirement[b]	Leucine intake[c] (whole natural protein)	Energy requirement[d]
Neonates	2.5–3.0 g/kg per day	80–150 mg/kg per day	120 (100–145) kcal/kg per day
Infants	2.0–3.0 g/kg per day	50–140 mg/kg per day	115 (95–145) kcal/kg per day
Young children	1.5–2.0 g/kg per day	500–900 mg per day	900–1800 kcal per day
Older children and adults	1.0–1.2 g/kg per day	650–1500 mg per day	1200–3900 kcal per day

[a] Modified from Acosta and Yannicelli 2001. These recommendations are only a guide and should be individualized for each patient, based on the severity of their disorder. Patients with milder forms of the disorder will tolerate a higher leucine intake and may only require a reduced natural protein diet

[b] Includes protein intake from special medical food devoid of leucine plus that from natural whole protein sources

[c] These figures reflect leucine intake if special medical foods devoid of leucine are used and may be too low for some actively growing infants and children

[d] Formula concentrations over 0.8 kcal/ml may result in loose stools, diarrhea, and dehydration

Close, frequent monitoring is needed for those patients on BCAA-, leucine-, or protein-restricted diets. Blood quantitative amino acid measurements should be done 2–4 h after a meal. The results should be available within a few days if not 48 h. Families and local health care personnel can be instructed in obtaining fingerstick dried blood filter paper or whole blood samples for quantitative amino acid measurements, which can be sent from their home or local community to testing laboratories between clinic visits. Changes in dietary recommendations need to be made and communicated to the family promptly after the levels are available. Frequent monitoring is needed in actively growing infants and young children, especially those on restricted diets, in whom increases in nutrient intake may need to be as high as 10% weekly. Using the rate of weight gain (grams per day), an estimate of the weight gain expected over the next week or prior to the next clinical monitoring may be made. The expected increase in weight should be taken into account when determining the amount of increase in nutrient intake needed in young infants so as not to fall behind growth requirements. Persistently low leucine levels can result in decreased appetite, poor feeding, lethargy, poor growth, weight loss, skin rashes, hair loss, and desquamation. With MSUD, deficiency of isoleucine and valine also may occur and result in symptoms similar to those of leucine deficiency. Older patients who discontinue the use of special medical foods yet continue to take a lowered protein intake without supplemental vitamins and minerals are at risk for multiple nutrient deficiencies.

Supplements of L-carnitine are used with the organic acidemias, but not with MSUD, to serve as a means for excretion of abnormal metabolites through the formation of acyl-carnitines and to prevent secondary L-carnitine deficiency. With IVA, glycine may be similarly given to promote the formation and excretion of isovalerylglycine (Fries et al. 1996, Naglak et al. 1988; Sousa et al. 1986). Cofactor therapy is employed with thiamine-responsive MSUD. In general, the remainder of the disorders are not vitamin- or cofactor-responsive. Intake of polyunsaturated omega-3 fatty acids and trace minerals may not be adequate with artificial diets and require supplementation. Those patients on reduced natural protein diets may also need supplements of multivitamin-mineral formulations and calcium.

Plans for sick-day management should be formulated for each patient and the family instructed to make these changes when the first signs of intercurrent illness or loss of metabolic control are noted. Often, the patient will respond to such measures and not progress to overt metabolic decompensation. Home monitoring of urine dinitrophenylhydrazine (DNPH) in MSUD and ketones in IVA may help guide clinical management. Families should be cautioned, however, that dilute urine samples may produce false-negative results. Evaluation of clinical symptoms remains of paramount importance.

Asymptomatic confirmed affected neonates, detected by newborn screening or due to a positive family history prior to clinical symptoms, should be treated as potentially developing an acute episode of metabolic decompensation and started on sick-day management. Intake of natural protein should be added slowly, with close monitoring.

Aggressive treatment is needed for those patients with overwhelming metabolic disease at their initial presentation, which most often occurs in the neonatal period. The patients are also at risk for similar episodes with intercurrent illnesses or increased protein intake for the remainder of their lives. Prevention of cerebral edema and correction of dehydration, hypoglycemia, and acidosis are critical to outcome (Berry et al. 1991; Strauss and Morton 2003; Thompson et al. 1990). Removal of toxic metabolites and reduction of high ammonia levels may require hemodialysis or hemofiltration (Jouvet et al. 2001). Treatment of an episode of acute, severe, metabolic decompensation is at times very difficult to manage, even for those experienced in treating such patients. Consultation with, if not referral to, an experienced center is recommended. Not all infants or children presenting with severe metabolic disease are rescued and survive. Those that do are often mentally and physically handicapped (Kaplan et al. 1991).

In addition to counseling concerning treatment and prognosis, families of affected individuals should receive genetic counseling concerning recurrence risks for subsequent children. Prenatal testing is available for most of the severe forms of the disorders. Carrier testing is variable and often depends upon the availability of DNA mutation analysis.

Other than MSUD and IVA, the remainder of the disorders of leucine metabolism are exceedingly rare and were only recognized and defined after

clinical organic acid determinations became available in the 1970s. The clinical experience in managing these cases is relatively limited and fragmented among the metabolic centers around the world. Thus, the recommendations for treatment, monitoring, and optimum outcome are still being defined. What is presented in this chapter should be considered only a basic guide for where to begin. With the advent of expanded newborn screening, additional cases will be identified, treated early, and hopefully add to our understanding of the pathophysiology of the disorders, and improve treatment and outcomes (Fig. 6.1).

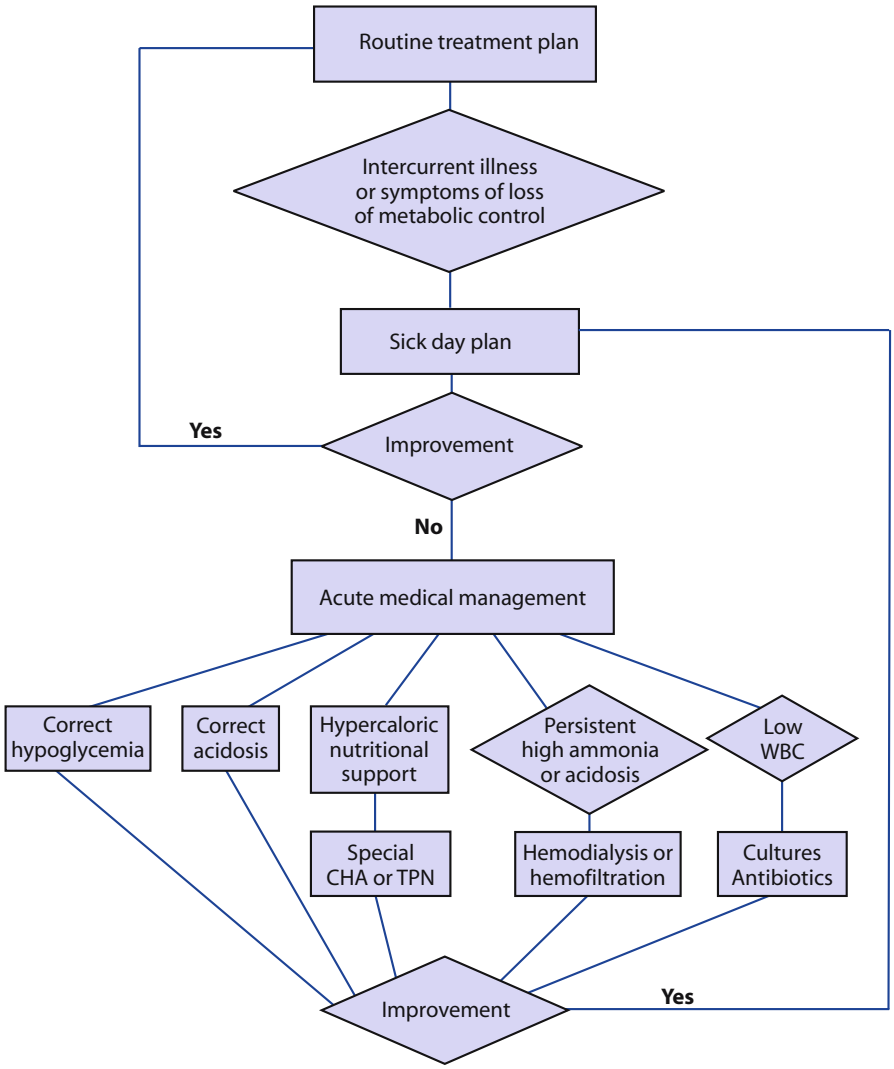

Fig. 6.1. Management of disorders of leucine metabolism

6.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
6.1	Maple syrup urine disease (MSUD; branched-chain α-ketoacid dehydrogenase complex, BCKDC, deficiency)			
6.1.1	Decarboxylase, E1 component α-subunit deficiency (MSUD 1A)	Elevation of all three branched-chain amino acids (BCAA): leucine, isoleucine, and valine Alloisoleucine present Leucine to alanine ratio > 0. 4 Elevated urine branched-chain α-ketoacids (BCKA): 2-oxoisocaproate, 2-oxo-3-methylvalerate, 2-oxoisovalerate, 2-hydroxyisovalerate, 2-hydroxyisocaproate, 2-hydroxy-3-methylvalerate	*BCKDHA*	248600
6.1.2	Decarboxylase, E1 component β-subunit deficiency (MSUD 1B)	See disorder 6.1.1.	*BCKDHB*	248611
6.1.3	Dihydrolipoyl acyl-transferase, E2 component deficiency (MSUD 2)	See disorder 6.1.1	*DBT*	248610
6.1.4	Lipoamide dehydrogenase, E3 component deficiency (combined deficiency of branched-chain α-ketoacid, pyruvate, and α-ketoglutarate dehydrogenase complexes; MSUD 3)	Elevated blood lactate, pyruvate, and alanine along with BCAA. Alloisoleucine present. Elevated urine lactate, pyruvate, 2-oxoglutarate, 2-hydroxyisovalerate, 2-hydroxyglutarate, and BCKA. See also Chap. 27	*DLD*	246900
6.2	Isovaleric acidemia (isovaleryl-CoA dehydrogenase deficiency)			
6.2.1	Classic isovaleric acidemia; isolated isovaleryl-CoA dehydrogenase deficiency (IVA)	Elevated plasma or serum isovaleric acid and urine isovalerylglycine	*IVA*	243500
6.2.2	Part of multiple acyl-CoA dehydrogenase deficiency	See Chap. 14		
6.3	3-Methylcrotonyl-CoA carboxylase (3MCCC) deficiency			
6.3.1	Isolated, biotin-unresponsive 3MCCC deficiency; subunit-1 deficiency (3MCCC1)	Elevated urine 3-methylcrotonylglycine and 3-hydroxyisovaleric acid.	*MCCC1*	210200
6.3.2	Isolated, biotin-unresponsive 3MCCC deficiency; subunit-2 deficiency. (3MCCC2)	See disorder 6.3.1	*MCCC2*	210210
6.3.3	Part of multiple CoA carboxylase deficiency, secondary to biotinidase or holocarboxylase deficiencies	See Chap. 7		

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
6.4	3-Methylglutaconic aciduria, type 1. (3-methylglutaconyl-CoA hydratase deficiency; 3MGI)	Elevated urine 3-methylglutaconic, 3-methylglutaric, and 3-hydroxyisovaleric acids	*AUH*	2650950
6.5	3-Hydroxy-3-methylglutaric aciduria (3-hydroxy-3-methyl-glutaryl, HMG, -CoA lyase deficiency; HMGCL)	Elevated urine 3-hydroxy-3-methyl-glutaric, 3-methylglutaconic, 3-methylglutaric, and 3-hydroxy-isovaleric acids, and occasionally 3-methylcrotonylglycine	*HMGCL*	246450

No.	Symbol	Age	Medication/diet	Dosage	Target plasma amino acid levels
6.1.1–6.1.3	MSUD 1A MSUD 1B MSUD 2 (severe forms)	All ages	Lowered BCAA diet[a] Isoleucine and valine supplements[b] Glutamine/alanine NaCl Thiamine[c]	 Adjusted to blood levels 100–250 mg/kg per day each 3–5 mEq/kg per day 10 mg/kg per day (50–300 mg/day)	Leucine 150–300 μM Isoleucine 150–300 μM Valine 200–400 μM[f]
6.1.1, 6.1.3	MSUD 1A MSUD 2 (milder forms)	All ages	Reduced natural protein diet[d] Multivitamin with minerals daily Thiamine[c]	 10 mg/kg per day (50–300 mg/day)	Within normal limits for age for the laboratory
6.1.3	MSUD 2 (thiamine-responsive form)	All ages	Reduced natural protein diet[d] Multivitamin with minerals daily Thiamine	 10 mg/kg per day (50–1000 mg/day)	Within normal limits for age for the laboratory
6.1.4	MSUD 3 (combined dehydrogenases deficiency)	All ages	See disorders 6.1.1–6.1.3 (severe forms)[e]		See disorders 6.1.1–6.1.3

[a] Special medical food devoid of the branched-chain amino acids

[b] As 10 mg/ml solutions. Leucine supplements also may be needed during the 1st year of life

[c] Thiamine given until molecular genotype known; not given if the patient is Mennonite

[d] Protein intake of approximately 1.5–2.0 g/kg body weight/day in young infants and 0.6–1.5 g/kg body weight/day in older children and adults

[e] Attempts at treatment with diet and cofactors have been unsuccessful in preventing CNS deterioration; thiamine not given

[f] Target ratios of approximately 1:1:2 for leucine, isoleucine, and valine, respectively

6.3 Treatment

■ *6.1 Branched-chain α-ketoacid dehydrogenase complex deficiency*

6.1.1 MSUD 1A
6.1.2 MSUD 1B
6.1.3 MSUD 2
6.1.4 MSUD 3

● *6.1.1–6.1.4 Treatment – Comments/Additions*

1. Intake of whole protein and supplements of individual amino acids are adjusted based on plasma quantitative amino acids levels to meet the target levels.
2. All patients with MSUD 1A, MSUD 1B, and MSUD 2 should be given a trial of thiamine therapy for at least 3 weeks, or until the molecular genotype is known. Patients homozygous for the Y393N Mennonite mutation are not thiamine-responsive.

6.2.1 Classic isovaleric acidemia

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.2.1	IVA (severe forms)	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
			L-Carnitine	100 mg/kg per day in 3–4 doses[c]	Normal range for laboratory
			Glycine	250 (150–300) mg/kg per day[c,d]	Glycine 200–400 µM
6.2.1	IVA (mild forms)	All ages	Reduced natural protein diet[b]		
			Multivitamin with minerals	Daily	
			L-Carnitine	100 mg/kg per day in 3–4 doses[c]	Normal range for laboratory
			Glycine	250 (150–300) mg/kg per day[d]	Glycine 200–400 µM

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used

[b] Protein intake of approximately 1.5–2.0 g/kg body weight per day in young infants and 0.6–1.5 g/kg body weight per day in older children and adults

[c] Calculate the amount present in the special medical food or protein-free product and add supplements to this to meet the recommended intake

[d] Glycine is added to the daily special formula as weighed dry powder or 100 mg/ml solution

6.2.1 Treatment – Comments/Additions

1. Although leucine is the precursor amino acid for the disorder, it is the organic acids that are toxic to the patients and not the leucine per se as with MSUD. Monitoring leucine levels gives an indication as to whether there is sufficient intake of natural protein to support growth and tissue repair. The plasma leucine range of 50–150 µM, however, may be too low for some growing infants and children. Many affected patients are able to tolerate a near-normal leucine intake and may be treated with a lowered natural protein diet, without selective leucine restriction. The least restrictive dietary approach should be used order to avoid overtreatment and leucine deficiency.

6.3.1–6.3.2 Isolated 3-methylcrotonyl-CoA carboxylase deficiency

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.3.1	3MCCC1	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
	3MCCC2		L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used. Glycine is not given
[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

6.3.1 Treatment – Comments/Additions

1. See comment 1 for disorder 6.2.1.
2. Patients are not responsive to biotin therapy.
3. Recently, asymptomatic children and adults have been found to have 3MCCC deficiency when family studies are done. These patients may not need dietary restrictions or L-carnitine, but may occasionally need blood and urine monitoring.

6.4 3-Methylglutaconic aciduria, type I

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.4	3MGI	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
			L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used. Glycine is not given
[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

6.4 Treatment-Comments/Additions

1. See comment 1 for disorder 6.2.1.

■ *6.5 3-Hydroxy-3-methylglutaric aciduria*

No.	Symbol	Age	Medication/diet	Dosage	Target plasma amino acid levels
6.5	HMGCL	All ages	Lowered leucine and fat diet[a]	Fat is limited to 20–25% of total daily caloric intake	Leucine 50–150 µM, or normal range for the laboratory
			L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake and low fat diet. The least restrictive diet should be used. Glycine is not given

[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

● *6.5 Comments/Additions*

1. See also comment 1 for disorder 6.2.1.
2. In addition to leucine restriction, daily caloric intake of fat is limited to 20–25% of total caloric intake per day. Use a protein-free product that contains carbohydrates and other nutrients, but no or very low fat.
3. Avoid fasting. Overnight drip nasogastric or gastrostomy feedings may be needed.
4. Uncooked cornstarch slurries or uncooked cornstarch added to the special metabolic formula may be used to prevent hypoglycemia.

6.4 Alternative Therapies/Experimental Trials

None known at present time.

6.5 Follow-up/Monitoring

6.1.1 MSUD 1A (severe forms)
6.1.2 MSUD 1B
6.1.3 MSUD 2 (severe forms)
6.1.4 MSUD 3

Age	Clinical monitoring: growth (weight, height, head circumference)[a]	Biochemical monitoring: blood quantitative amino acid levels[b]	Other[c]
Neonates	Weekly	Twice weekly to weekly	Every 1–3 months
Young infants	Weekly	Weekly to every 2 weeks	Every 1–3 months
Older infants and children	Every 1–3 months	Every 2 weeks to monthly	Every 3 months
Older children and adults	Every 1–3 months	Every 1–3 months	Every 6–12 months

This schedule is only a guide for those patients using special medical food devoid of leucine. Monitoring should be individualized for each patient, based on the severity of their disorder. Less frequent monitoring is needed for patients on a reduced natural protein diet

[a] Growth parameters may be obtained in the local physician's office and sent to the metabolic center after early infancy

[b] Blood amino acid levels should be determined by a quantitative method and the results include a total panel. Nutrient intake should be evaluated with each determination and appropriate and prompt changes made to the dietary prescription. Fingerstick dried blood filter paper or whole-blood samples may be obtained by the family or local health care providers and sent to testing laboratories between clinic visits

[c] The frequency and type of testing done for follow-up monitoring varies between metabolic clinics. As appropriate, the following testing may be considered. Complete blood count with differential, total protein, albumin, and protein stores (prealbumin, retinol-binding protein, transferrin, and/or transthyretin). Urine DNPH spot tests should be monitored daily at home in young infants as treatment is initiated, then weekly in young infants, and as indicated in older children and adults. Urine DNPH should be measured more frequently after diet changes or with signs of intercurrent illness. Monitor erythrocyte lipid composition, zinc, and serum iron/TIBC every 3 months when younger, every 6–12 months when older

■ Standard Protocol for Intercurrent Illness

● *Initial Measures*

Step	Branched-chain amino acid-free special medical food	Natural high-quality protein addition to special formula mix	Natural food leucine intake
1	1.2–1.5 times usual daily amount with extra added isoleucine and valine[a]	None	None
2	1.2–1.5 times daily amount with added isoleucine and valine[a]	One-half usual dietary intake	None to half usual dietary intake
3	Usual daily amount with well-day additions of isoleucine and valine	Full dietary intake	Gradual increase to usual full dietary intake

This plan should be individualized for each patient, based on the degree of severity of their disorder and blood quantitative amino acid levels. The exact products and measures (g) should be recorded, shared with the family, and periodically updated as the patient grows

[a] Additions of isoleucine and valine should be increased during sick days and be approximately equivalent to the patient's usual daily intake of these two amino acids from table foods and high-quality protein (milk, formula). Solutions are 10 mg/ml. The goal is to keep levels of isoleucine and valine above 400–600 μM

● *6.1.1–6.1.4 Intercurrent Illness – Comments/Additions*

A. Families/individuals should start sick-day formula (to decrease leucine intake, increase isoleucine and valine intake, and suppress catabolism) with the onset of intercurrent illness or symptoms related to loss of metabolic control. Fluids without calories or electrolytes should be avoided, or intake minimized.
B. Monitor urine DNPH, which will become positive with loss of metabolic control or inadequate caloric intake.
C. Ondansetron may be given for nausea/emesis (0.15 mg/kg per dose q 4–8 h).
D. If the patient is unable to take in oral fluids, has persistent vomiting, or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

■ Acute Emergency Management: (Includes Management of Ill Neonates)

Clinical finding	Treatment
1. Dehydration	IV D10/W with 155 mEq/l NaCl and 20 mEq/l KCl (if adequate renal output) at maintenance until CNS status established. Normal saline bolus may be given, if indicated, as 10 ml/kg over 1 h in addition to the glucose-containing fluids
2. Hypoglycemia	10% dextrose, 1–2 ml/kg per dose (max 5–10 ml/kg) slow IV push
3. Acidosis	Sodium bicarbonate, 1–2 mEq/kg drip over 20–30 min, diluted with IV fluids. May repeat. Part or all of sodium in IV fluids may be replaced with sodium bicarbonate in severely acidotic patients (maximum total sodium concentration 155 mEq/l)
4. Maintain normal serum sodium and osmolality levels	(a) Monitor intake and output, body weight, urine specific gravity (b) 3% NaCl, dosage carefully calculated to replace deficit if hyponatremic. May also need furosemide 0.25–0.50 mg/kg per dose every 6–8 h if receives too much free water or serum osmolality falls (c) Mannitol 0.5 g/kg per dose, as indicated
5. Blood glucose > 200 mg/dl	Regular insulin drip, 0.05–0.10 units/kg per h
6. Increase calories to suppress catabolism	(a) Give step 1 sick-day diet by PO or NG/G-tube[b] (b) 20% fat emulsion, rate 1 ml per each 4 ml D10/W IV (c) If NPO use lowered BCAA mixture for CHA/TPN
7. Persistent elevated leucine levels or hyperammonemia	(a) Hemodialysis or continuous venovenous hemofiltration (CVVH) usually not needed, but if done should be *in addition* to measures in 6 (b) IV propranolol, to suppress catecholamines

This plan should be individualized for each patient, based on the severity and type of their disorder

[a] Supplements of isoleucine and valine are not given initially if blood levels are markedly elevated for all three BCAA, i. e., presenting episode. They usually need to added at 2–3 days into therapy

● *6.1.1–6.1.4 (severe forms) Acute Emergency Management – Comments/Additions*

A. Obtain a clinical history and perform an examination promptly on arrival of the patient, to assess the etiology of the intercurrent illness and determine the clinical status. Specific attention should be made to the degree of hydration and presence of signs of encephalopathy or cerebral edema (odor of maple syrup, altered respiratory rate and type, perfusion, lethargy, stupor, coma). Stop all protein sources.
B. Obtain baseline laboratory studies to include Dextrostix, blood glucose, electrolytes, CO_2, ammonia, and any other laboratory tests indicated by the clinical history and examination.
C. Monitor blood quantitative amino acid levels at least daily. Expect rate of decrease in leucine levels to approach 750 M/day. Isoleucine and valine levels should be high, at more than 400–600 M to suppress entry of leucine into the brain. Monitor urine DNPH at least daily; persistent positive testing may occur with elevated isoleucine levels however.
D. Carefully observe patients for pancreatitis, which may occur on the 2nd or 3rd day of hospitalization as leucine levels are returning to normal.
E. Patients with the E3 subunit deficiency may experience severe lactic acidosis and hypoglycemia.

6.1.1 MSUD 1A (mild forms)
6.1.2 MSUD 2 (mild forms)

● *6.1.1–6.1.2 (mild forms) Follow-up/Monitoring – Comment/Additions*

1. Monitoring may be less frequent than for severe forms of MSUD.

■ Standard Protocol for Intercurrent Illness

1. Most patients do not become as seriously ill as in classic MSUD, but the same general approach to care applies while they are ill.

6.2.1 Classic isovaleric acidemia
6.3.1–6.3.2 Isolated 3-methylcrotonyl-CoA carboxylase deficiency
6.4 3-Methylglutaconic aciduria, type I
6.5 3-Hydroxy-3-methylglutaric aciduria

Age	Clinical monitoring	Biochemical monitoring		Other[d]
	Growth (weight, height, head circumference)[a]	Blood quantitative amino acid levels[b]	Urine organic acids[c]	
Neonates	Weekly	Weekly	Every 1–3 months	Every 1–3 months
Young infants	Weekly to every 2 weeks	Every 2 weeks	Every 1–3 months	Every 1–3 months
Older infants and young children	Monthly	Every 1–3 months	Every 3 months	Every 3 months
Older children and adults	Every 6–12 months.	Every 6–12 months	Every 6–12 months	Every 6–12 months

This schedule is only a guide for patients with severe forms of the disorders. It should be individualized for each patient, based on the severity of their disorder. Less frequent monitoring is needed for patients on reduced natural protein diets, not taking special medical foods devoid of leucine

[a] Growth parameters may be obtained in the local physician's office and sent to the metabolic center after early infancy

[b] Blood quantitative amino acid levels should be determined by a quantitative method and the results include a total panel. Nutrient intake should be monitored with each determination and appropriate and prompt changes made to the dietary prescription. Levels may need to be done more frequently when initiating therapy. Fingerstick dried blood filter paper or whole-blood samples may be obtained by the family or local health care providers and sent to testing laboratories between clinic visits.

[c] Monitor pattern and amount of abnormal organic acids present and compare with clinical status for the individual patient, i. e., elevated levels of 3-hydroxyisovalerate may indicate lack of complete metabolic control

[d] The frequency and type of testing done for follow-up monitoring varies between metabolic clinics. As appropriate, the following testing may be considered. Complete blood count with differential and platelet count, electrolytes with CO_2, glucose, total protein, albumin, calcium, phosphorus, zinc, and protein stores (prealbumin, retinol-binding protein, transferrin, and/or transthyretin). Free carnitine and total carnitine levels, iron/TIBC or ferritin, zinc, and erythrocyte lipid composition every 3 months under 1 year of age, then twice yearly. Urine ketones should be monitored at home daily when initiating therapy in infants, then weekly for young infants, and then intermittently, i. e., after diet changes or with signs of intercurrent illness or loss of metabolic control for older infants and children. Note that patients with HMGCL cannot make ketones.

Standard Protocol for Intercurrent Illness

Initial Measures

Step	Leucine-free special medical food[a]	Protein free special medical food	Natural food leucine intake	L-Carnitine
1	None	Supply at least usual dietary caloric intake	None	Double usual daily dose
2	One-half to full usual dietary intake	Add as needed to supply at least usual dietary caloric intake	None	Double usual daily dose
3	Usual dietary intake	Add as needed to supply usual dietary caloric intake	Gradual increase to usual dietary intake	Routine dose

This plan should be individualized for each patient, based on the degree of severity of their disorder. Mildly affected patients may go directly to step 2 and skip step 1. Step 1 should not be used for more than a few days or protein mobilization may occur. For sensitive, severely affected patients, multiple substeps will be needed in steps 2 and 3. The exact products and measures (g) should be recorded, shared with the family, and updated as the patient grows

[a] Leucine-free and low fat for HMGCL

- *6.2–6.5 Intercurrent Illness – Comments/Additions*

A. Families/individuals should start sick-day formula (to decrease leucine intake and suppress catabolism) and increase the L-carnitine dose with the onset of intercurrent illness or symptoms related to loss of metabolic control. Fluids without calories or electrolytes should be avoided, or intake minimized.
B. Monitor urine ketones, which will become positive with loss of metabolic control or inadequate caloric intake. The exception is in patients with HMGCL deficiency, who are unable to make ketones. Monitoring urine ketones in this disorder is uninformative.
C. Ondansetron may be given for nausea/emesis (0.15 mg/kg/dose q 4–8 h).
D. If the patient is unable to take in oral fluids, has persistent vomiting, or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

- *Acute Emergency Management: (Includes Management of Ill Neonates)*

Clinical finding	Treatment
1. Dehydration	IV D10/W with 75 mEq/l NaCl and 20 mEq/l KCl (if adequate renal output) at 1.2–1.5 times maintenance. Normal saline bolus may be given, if indicated, as 10 ml/kg over 1 h in addition to the glucose-containing fluids
2. Hypoglycemia	10% dextrose, 1–2 ml/kg/dose (max 5–10 ml/kg) slow IV push
3. Acidosis	Sodium bicarbonate, 1–2 mEq/kg drip over 20–30 min, diluted with IV fluids. May repeat. Part or all of sodium in IV fluids may be replaced with sodium bicarbonate in severely acidotic patients (maximum total sodium concentration 155 mEq/l)
4. Maintain normal serum sodium and osmolality levels	(a) Monitor intake and output, body weight, urine specific gravity (b) 3% NaCl, dosage carefully calculated to replace deficit if hyponatremic. May also need furosemide 0.25–0.50 mg/kg per dose every 6–8 h, if receives too much free water or serum osmolality falls (c) Mannitol 0.5 g/kg per dose, if indicated
5. IV L-carnitine	100 mg/kg per day in 4–6 divided doses, slow IV bolus over 20–30 min
6. Blood glucose > 200 mg/dl	Regular insulin drip, 0.05–0.10 units/kg per h
7. Increase calories to suppress catabolism	(a) Give step 1 sick-day diet by PO or NG/G-tube (b) 20% fat emulsion, rate 1 ml per each 4 ml D10/W IV (*Do Not give with HMGCL*) (c) If NPO use lowered leucine amino acid mixture for CHA/TPN
8. Glycine (IVA only)	Usual daily dose in sick-day enteral formula or in special amino acid mixture for CHA/TPN
9. Neutropenia, thrombocytopenia	Body fluid cultures, antibiotics
10. Persistent acidosis or hyperammonemia	Hemodialysis or continuous venovenous hemofiltration (CVVH) *in addition* to 7

This plan should be individualized for each patient, based on the clinical findings at the time of the episode

- *6.2–6.5 Acute Emergency Management – Comments/Additions*

A. Obtain a clinical history and perform an examination promptly on arrival of the patient, to assess the etiology of the intercurrent illness and determine the clinical status. Specific attention should be made to the degree of hydration and presence of signs of acidosis, hypoglycemia, or hyperammonemia (odor of sweaty feet, altered respiratory rate and type, perfusion, lethargy, stupor, coma). Stop all protein sources.
B. Obtain baseline laboratory studies to include Dextrostix, blood glucose, electrolytes, CO_2, ammonia, and any other laboratory tests indicated by the clinical history and examination.
C. Monitor serial blood levels of electrolytes with CO_2, osmolality, and ammonia; urine specific gravity and ketones; fluid intake and output, body weight.

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