Disorders of Leucine, Isoleucine, and Valine Metabolism

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Summary

Disorders in the catabolic pathways of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine encompass diverse organic and aminoacidurias. Clinical severity may range from asymptomatic findings in some to life-threatening episodes and multiorgan involvement in others. Several of these defects reflect a complex pathogenesis related to mitochondrial dysfunction, particularly the 3-methylglutaconic acidurias. As a general rule, treatment includes the following: (1) dietary restriction of the precursor BCAA along with optimal nutritional supply, (2) adjunct therapy (e.g., with L-carnitine, appropriate cofactors, other conjugating compounds), (3) rapid intervention for metabolic decompensation. Late complications of these diseases must be anticipated, such as liver and renal failure. In asymptomatic individuals, instructions regarding risks for metabolic stress and fasting avoidance, along with clinical monitoring, represent appropriate prophylactic interventions at this time.

7.1 Introduction

The catabolic pathways of branched-chain amino acids (BCAA), namely, leucine, isoleucine, and valine, consist of multiple steps including transamination, oxidative decarboxylation, and dehydrogenation. Due to irreversible steps early in metabolism, 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, these disorders are associated with organic academia and aciduria. Severe forms of these disorders usually present as acute, overwhelming illness in the neonatal period if not detected through newborn screening. Milder variants may be episodic and not become symptomatic until late childhood or even adult life. Moreover, some patients are asymptomatic and identified only through family studies or newborn screening. Some disorders of BCAA metabolism are exceedingly rare, and the clinical experience in managing these cases is still being defined.

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N. Blau et al. (eds.), *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*,
DOI 10.1007/978-3-642-40337-8_7,

The existence of *branched-chain amino acid* (*BCAA*) *transferase* (*BCAT1 and BCAT2*) *deficiency* in humans remains in question. There is some evidence that transamination of valine and transamination of leucine and isoleucine may be affected differentially. Early reports have described patients with hyperleucine-isoleucinemia and hypervalinemia, attributed to a defect of branched-chain amino acid transamination, who presented with failure to thrive and mental retardation (Reddi et al. 1977).

Maple syrup urine disease (MSUD) results from deficient activity of the branched-chain α-keto acid dehydrogenase complex (BCKDC). During episodes of metabolic decompensation, the BCAA and their corresponding branched-chain α-keto acids (BCKA) accumulate excessively. The pathophysiology of MSUD is thought to be related primarily to leucine (Knerr et al. 2012). The enzyme complex BCKDC consists of three catalytic components (E1, E2, and E3) encoded by four different genetic loci. Mutations in all four of the catalytic loci have been associated with clinical disease (MSUD 1A, 1B, 2, 3, respectively).

Five *clinical forms* of MSUD exist, differentiated by the amount of residual enzymatic activity, age and severity of onset, and responsiveness to thiamine. These include *classic*, *intermediate*, *intermittent*, and *thiamine-responsive* MSUD, in addition to *E3* (lipoamide dehydrogenase) *deficiency*. The latter associates with combined deficiencies of the pyruvate dehydrogenase complex and 2-oxoglutarate dehydrogenase complexes, which share the E3 component with BCKDC.

Isovaleric acidemia (IVA) results from deficient activity of isovaleryl-CoA dehydrogenase, ranging from acute neonatal to an intermittent or chronic presentation. Asymptomatic individuals with only subtle biochemical abnormalities are detected through newborn screening (Vockley and Ensenauer 2006; Ensenauer et al. 2004). In patients with a severe phenotype, the odor of "sweaty feet" may be detected during metabolic crisis, associated with marked ketoacidosis, bone marrow suppression, and hyperammonemia.

3-*Methylcrotonyl-CoA carboxylase* (*3MCCC*) *deficiency* (*MCCD*) also features a highly variable phenotype, from severe to asymptomatic presentation in patients detected via newborn screening or family association studies (Gibson et al. 1998). Thus far, there are no reliable markers to identify the few individuals at risk for clinical symptoms. Appropriate testing (urinary organic acids, acylcarnitine profile, and eventually mutation analysis/enzymatic assay) is necessary to differentiate 3MCCC deficiency from the multiple carboxylase deficiencies due to defects in biotin metabolism (Chap. 14).

3-Methylglutaconic aciduria may occur in multiple forms. Only type I (MGA1), associated with reduced activity of 3-methylglutaconyl-CoA hydratase, is a disorder of the leucine degradation pathway. Barth (MGA2) syndrome is an X-linked multisystem disorder with cardiomyopathy, myopathy, neutropenia, and 3-methylglutaconic aciduria. Costeff syndrome (MGA3) is characterized by optic atrophy and neurological symptoms. MEGDEL syndrome is a recessive disorder featuring sensorineural deafness and encephalopathy with neuroradiological evidence of Leigh disease. Neonatal mitochondrial encephalocardiomyopathy is caused by isolated mitochondrial ATP synthase deficiency, associated with mutation in the TMEM 70 gene. 3-Methylglutaconic aciduria type IV refers to conditions in which the primary etiologies remain to be elucidated.

3-Hydroxy-3-methylglutaric acidemia (*HMG-CoA lyase deficiency*) is a dual defect in leucine degradation and ketogenesis that often presents with neonatal hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia (Gibson et al. 1988). Milder forms of the disorder, including presentation in adulthood, have also been reported. Overwhelming metabolic decompensation and organic aciduria is associated with a characteristic absence of ketone bodies, a hallmark of this disorder.

2-Methylbutyrylglycinuria or 2-methylbutyryl-CoA dehydrogenase (*MBD*) *deficiency* is a defect in isoleucine degradation caused by short/branched-chain acyl-CoA dehydrogenase (SBCAD) deficiency (Andresen et al. 2000). Diverse clinical symptoms such as hypotonia, mental retardation, autistic features, hypoglycemia, or metabolic acidosis have been reported, but most individuals (especially those identified by newborn screening) have remained asymptomatic (Gibson et al. 2000; Sass et al. 2008). A founder mutation in the Hmong Chinese population has been described (Alfardan et al. 2010; Matern et al. 2003).

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (*MHBD*) *deficiency* (*or 17beta-hydroxysteroid dehydrogenase type 10* (*HSD10*) *deficiency*) was first reported in a 2-year-old boy with neurodegenerative symptoms (Zschocke et al. 2000). This defect was also documented in a female patient who was less severely affected, suggesting skewed X-inactivation (Perez-Cerda et al. 2005). The disease-causing gene, HSD17B10, encodes 17beta-hydroxysteroid dehydrogenase type 10 (HSD10), the latter essential for structural and functional integrity of mitochondria (Rauschenberger et al. 2010).

Beta-ketothiolase deficiency (*alpha-methylacetoacetic aciduria*, *3-oxothiolase deficiency*) is associated with recurrent episodes of vomiting, ketosis, and metabolic acidosis. Hypoglycemia, neutropenia, and thrombocytopenia have been observed in infants.

Isobutyryl-CoA dehydrogenase deficiency (*IBD deficiency*) is a disorder of valine degradation. The original patient presented with anemia and dilated cardiomyopathy (Roe et al. 1998). Thus far, at least 22 individuals have been

described who are mostly asymptomatic, largely identified via newborn screening (Koeberl et al. 2003; Sass et al. 2004; Oglesbee et al. 2007).

3-Hydroxyisobutyryl-CoA deacylase deficiency (*or methacrylic aciduria*) has been confirmed in only two patients. They presented with failure to thrive, developmental delay, and neurological symptoms in infancy. One patient had congenital malformations including vertebral abnormalities, tetralogy of Fallot, and agenesis of the corpus callosum and died at 3 months. A second patient had episodes of ketoacidosis and an abnormal brain MRI with signal abnormalities in the globi pallidi and in the midbrain. Unusual cysteine and cysteamine conjugates of methacrylic acid were detected in urine. In fibroblasts from both patients, 3-hydroxyisobutyryl-CoA hydrolase activity was deficient and molecular analysis revealed mutations in the HIBCH gene (Loupatty et al. 2007).

3-Hydroxyisobutyric aciduria may be caused by a primary defect of 3-hydroxyisobutyrate dehydrogenase, active in valine metabolism, or via secondary inhibition of 3-hydroxyisobutyrate dehydrogenase in selected respiratory chain defects (Loupatty et al. 2006). The clinical phenotype is variable, but the majority of patients reported in the literature presented with dysmorphic features, neurodevelopmental symptoms, encephalopathy, ketoacidotic episodes, and lactic acidemia.

Methylmalonate semialdehyde dehydrogenase (*MMSDH*) *deficiency* is a rare disorder of the valine catabolic pathway associated with vomiting and dehydration. So far, only one patient has had a mutation identified in the MMSDH gene (Chambliss et al. 2000).

Isoleucine and valine share the propionate pathway for their terminal steps of catabolism, and *propionic acidemia* (PA, propionyl-CoA carboxylase deficiency) and *methylmalonic acidemia* (MMA, methylmalonyl-CoA mutase deficiency) are disorders of propionate degradation derived in part from the catabolism of isoleucine and valine, as well as other propionate precursors (threonine, methionine, odd-chain fatty acids, and cholesterol). PA usually presents with life-threatening episodes of ketoacidosis, hyperammonemia, encephalopathy, and hematological manifestations. Late complications of these disorders include renal failure (particularly in MMA), cardiomyopathy, long QT syndrome, basal ganglion infarction, optic neuropathy, or impaired hearing ability (particularly in PA) (Grünert et al. 2013). Respiratory chain deficiencies have been demonstrated in both disorders (De Keyzer et al. 2009). In addition to the primary deficiencies of propionyl-CoA carboxylase (PCC) and methylmalonyl-CoA mutase (MUT), secondary defects of these enzymes can be associated with genetic disorders in the metabolism of their cofactors, including biotin (Chap. 14) and cobalamin (Chap. 13).

Malonic aciduria (MA) is caused by malonyl-CoA decarboxylase deficiency leading to a block in fatty acid metabolism. Patients may present with cardiomyopathy, developmental delay, short stature, seizures, hypoglycemia, and metabolic acidosis (Salomons et al. 2007).

Combined malonic and methylmalonic aciduria (CMAMMA) is a rare recessive disorder caused by a defect in the ACSF3 gene which encodes an acyl-CoA synthetase. Patients present with developmental delay, seizures, cognitive decline, cardiomyopathy, and metabolic acidosis.

7.2 Nomenclature

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
7.1	BCAA aminotransferase deficiency	BCAA transaminase	BCAT	*BAT*		BCAA aminotransferase	238340	All forms
7.2	Maple syrup urine disease	Branched-chain alpha-keto acid dehydrogenase complex deficiency	MSUD	*BCKDHA*; *BCKDHB*; *DBT*; *DLD*	19q13.1–13.2; 6q14.1; 7q31–q32; 1p31	Branched-chain alpha-keto acid dehydrogenase complex	248600	All forms
7.3	Isovaleric acidemia	Isovaleryl-CoA dehydrogenase deficiency	IVA	*ACAD2*	15q14–q15	Isovaleryl-CoA dehydrogenase	243500	All forms
7.4	Methylcrotonylglycinuria	Methylcrotonyl-CoA carboxylase deficiency	MCC A; MCC B	*MCCC1*; *MCCC2*	3q27; 5q12–13.2	Methylcrotonyl-CoA carboxylase	210200	All forms
7.5	Methylglutaconic aciduria type I	3-Methylglutaconyl-CoA hydratase deficiency	MGA1	*AUH*	9q22.31	3-Methylglutaconyl-CoA hydratase	250950	All forms
7.6	Barth syndrome	Methylglutaconic aciduria type II	MGA2		Xq28	Taffazin	302060	All forms
7.7	MEGDEL syndrome		MEGDEL	*SERAC1*	6q25.3	MEGDEL	614739	All forms
7.8	Neonatal mitochondrial encephalocardiomyopathy		NME	*TMEM70*	8q21.11	Complex V assembly protein	614052	All forms
7.9	Costeff syndrome	Methylglutaconic aciduria type III	MGA3	*OPA3*	19q13.2–13.3	OPA3 protein	258501	All forms
7.10	Methylglutaconic aciduria type IV	3-Methylglutaconic aciduria	MGA4			?	250951	Idiopathic
7.11	3-Hydroxy-3-methylglutaric aciduria	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	HMGCL	*HMGCL*	1p35–36	3-Hydroxy-3-methylglutaryl-CoA lyase	246450	All forms
7.12	2-Methylbutyrylglycinuria	2-Methylbutyryl-CoA dehydrogenase deficiency	MBCD	*ACADSB*	10q26.13	2-Methylbutyryl-CoA dehydrogenase	610006	All forms
7.13	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency	17-beta-hydroxysteroid dehydrogenase type 10 deficiency	HSD10	*HSD17B10*	Xp11.2	17-Beta-hydroxysteroid dehydrogenase type 10	300438	All forms
7.14	Alpha-methylacetoacetic aciduria	Beta-Ketothiolase deficiency	BKT	*HADHB*	2p23	3-Oxothiolas	203750	All forms
7.15	Isobutyryl-CoA dehydrogenase deficiency	Isobutyrylglycinuria	IBD	*ACAD8*	11q25	Isobutyryl-CoA dehydrogenase	611283	All forms
7.16	3-Hydroxyisobutyryl-CoA deacylase deficiency	Methacrylic aciduria	HIBCH deficiency	*HIBCH*	2q32.2	3-Hydroxyisobutyryl-CoA deacylase	250620	All forms
7.17	3-Hydroxyisobutyrate dehydrogenase deficiency	3-Hydroxyisobutyric aciduria	HIBADH deficiency	*HIBADH*	7p15.2	3-Hydroxyisobutyrate dehydrogenase	236795	All forms
7.18	Methylmalonate semialdehyde dehydrogenase deficiency	Combined semialdehyde dehydrogenase deficiency	MMSDH	*ALDH6A1*	14q24.3	Methylmalonate semialdehyde dehydrogenase	603178	All forms
7.19	Propionic acidemia	Propionyl-CoA carboxylase deficiency	PA	*PCCA*; *PCCB*	13q32; 3q21–q22	Propionyl-CoA carboxylase deficiency	232000	All forms
7.20	Methylmalonic acidemia	Methylmalonyl-CoA mutase deficiency	MMA	*MUT*	6p12.3	Methylmalonyl-CoA mutase	251000	Functional
7.21	Malonic aciduria	Malonyl-CoA decarboxylase deficiency	MA	*MLYCD*	16q24	Malonyl-CoA decarboxylase	248360	All forms
7.22	Combined MMA and MA		MMA/MA	*ACSF3*	16q24.3	Acetyl-CoA synthase family 3	614245	All forms

7.3 Metabolic Pathway

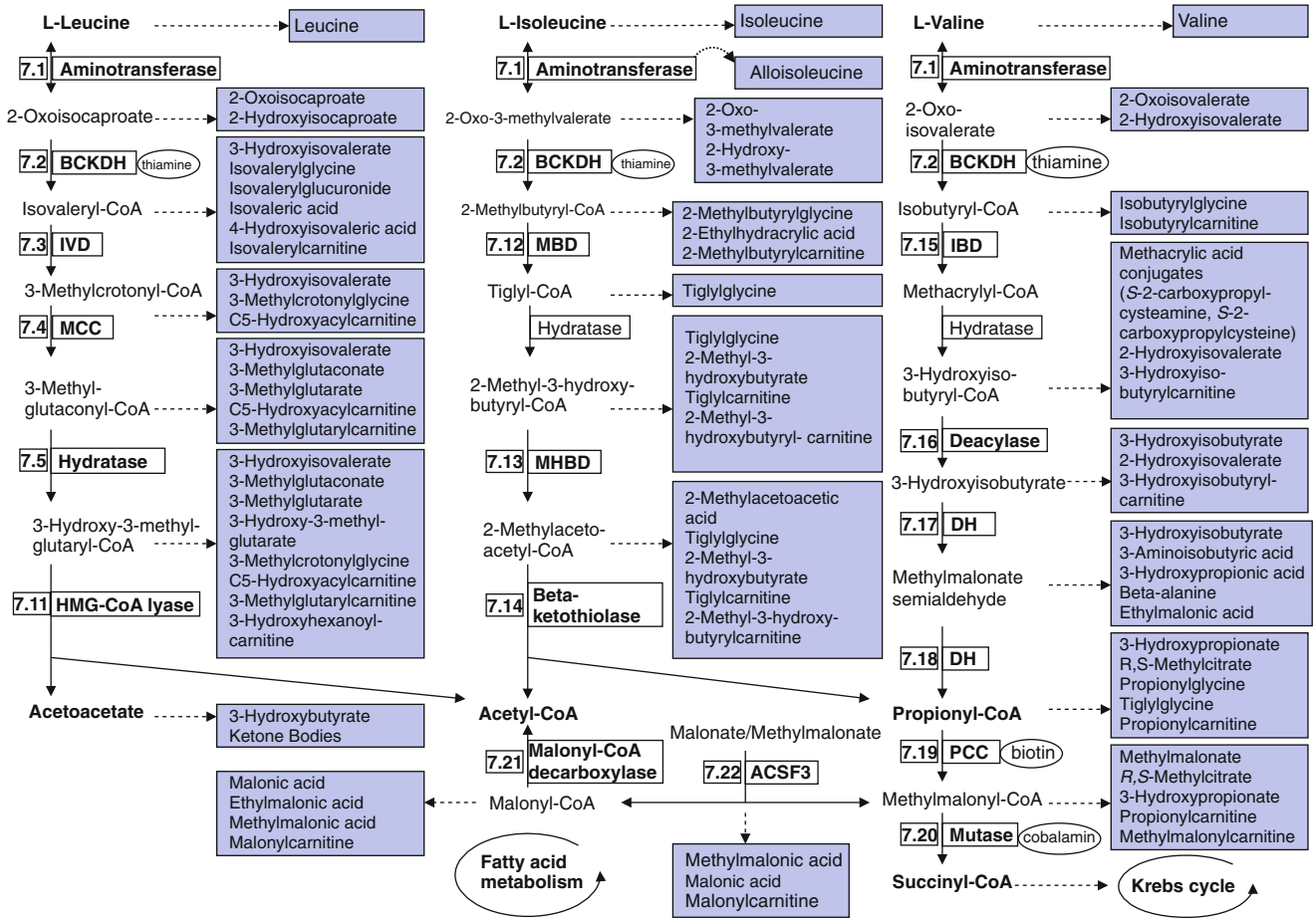

Fig. 7.1 Metabolic pathway

7.4 Signs and Symptoms

Table 7.1 BCAA aminotransferase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Hyperkinesia	±	±	±		
	Hypotonia	±	±	±		
	Movement, decreased spontaneously	±	±	±		
	Retardation, psychomotor	±	+	±		
Dermatological	Alopecia	±	±	±		
Digestive	**Failure to thrive**	±	+	±		
	Feeding difficulties	±	+	±		
	Vomiting, episodic	±	±	±		
Eye	Nystagmus	±	±	±		
Hair	Loss of hair	±	±	±		
Routine laboratory	Ketoacidosis	±	±	±		
	Metabolic acidosis	±	±	±		

(continued)

Table 7.1 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Acylcarnitines, all (P)	n	n	n		
	Allo-isoleucine (P)	n	n	n		
	Arginine (P)	n-↑↑	n-↑↑	n-↑↑		
	Glycine (P)	n-↑	n-↑	n-↑		
	Isoleucine (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑		
	Leucine (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑		
	Valine (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑		

Table 7.2 Maple syrup urine disease

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Apnea	±	±	±	±	±
	Ataxia	±	±	±	±	±
	Axonal sensory motor polyneuropathy, chronic	±	±	±	±	±
	Brain edema	±	±	±	±	±
	Brain edema, cytotoxic	±	±	±	±	±
	Dystonia	±	±	±	±	±
	Encephalopathic crisis, acute	±	±	±	±	±
	Hypo- or hypertonia	±	±	±	±	±
	Irritability, episodic	±	±	±	±	±
	Lethargy, coma (during ketoacidotic episodes)	+	+	+	+	+
	Opisthotonus	±	±	±	±	±
	Retardation, psychomotor	±	±	±	±	±
	Seizures	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Feeding difficulties	+	+	+	±	±
	Pancreatitis	±	±	±	±	±
	Vomiting, episodic	+	+	+	±	±
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±
Other	Hypothermia during crisis	±	±	±		
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Anion gap	+	+	+	+	+
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	+	+	+	+	+
	Metabolic acidosis	+	+	+	+	+
	Odor of maple syrup	±	±	±	±	±
	Osmolality (S)	↓-n	↓-n	↓-n	↓-n	↓-n
	Sodium (P)	↓-n	↓-n	↓-n	↓-n	↓-n
Special laboratory	2,4-Dinitrophenylhydrazine test (U)	±	±	±	±	±
	Allo-isoleucine (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	BCKDC activity (FB)	↓	↓	↓	↓	↓
	Branched-chain oxoacids (P, U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Ferric chloride test (U)	±	±	±	±	±
	Leu, Ile, Val (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	MRI: brain edema	±	±	±	±	±
	MRI: brainstem and cerebellar edema	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: deep gray matter structural lesions	±	±	±	±	±
	MRI: delayed myelination	±	±	±	±	±
	MRI: vacuolating myelinopathy	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
	MRS: low NAA peak during crisis	+	+	+	+	+

Table 7.3 Isovaleric acidemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiac arrhythmia	±	±	±	±	±
CNS	Altered consciousness	±	±	±	±	±
	Ataxia		±	±	±	±
	Developmental delay	±	±	±	±	±
	Encephalopathic crisis, acute	±	±	±	±	±
	Hypo- or hypertonia	±	±	±	±	±
	Lethargy, coma (during ketoacidotic episodes)	+	+	+	+	+
	Retardation, psychomotor	±	±	±	±	±
	Seizures	±	±	±	±	±
Dermatological	Alopecia		±	±		
Digestive	Failure to thrive	±	±	±	±	±
	Feeding difficulties	+	+	+	±	±
	Hepatomegaly	±	±	±	±	±
	Pancreatitis	±	±	±	±	±
	Vomiting, episodic	+	+	+	±	±
Hematological	Leukopenia	±	±	±	±	±
	Neutropenia	±	±	±	±	±
	Pancytopenia	±	±	±	±	±
	Thrombocytopenia	±	±	±	±	±
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±
Other	Hypothermia during crisis	±	±	±		
	Odor of sweaty feet	±	±	±	±	±
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Anion gap	+	+	+	+	+
	Calcium (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	+	+	+	+	+
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Metabolic acidosis	+	+	+	+	+
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	**3-Hydroxyisovaleric acid (U)**	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C5-Acylcarnitine (P, B)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Carnitine, esterfied (P)	↑	↑	↑	↑	↑
	Carnitine, free (DBS, P)	↓	↓	↓	↓	↓
	Glycine (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Isovaleric acid (P)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Isovaleryl-CoA dehydrogenase (FB)	↓	↓	↓	↓	↓
	Isovalerylglycine (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	MRI: abnormalities of the globus pallidus	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
	MRS: increased ratio of lactate to NAA	±	±	±	±	±

Table 7.4 Methylcrotonylglycinuria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy	±	±	±	±	±
CNS	Encephalopathy acute, precipitated by infection	±	±	±	±	±
	Hypo or hypertonia	±	±	±	±	±
	Metabolic stroke	±	±	±	±	±
	Retardation, psychomotor	±	±	±	±	±

(continued)

Table 7.4 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Digestive	Failure to thrive	±	±	±	±	±
Hematological	Neutropenia	±	±	±	±	±
	Thrombocytopenia	±	±	±	±	±
Musculoskeletal	Muscle pain.	±	±	±	±	±
	Muscle weakness	±	±	±	±	±
Other	Highly variable phenotype incl asymptomatic individuals	±	±	±	±	±
	Odor, acrid (Urine)	±	±	±	±	±
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Anion gap	±	±	±	±	±
	ASAT/ALAT (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Base excess	±	±	±	±	±
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	±	±	±	±	±
	Metabolic acidosis	±	±	±	±	±
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	3-Hydroxyisovaleric acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylcrotonylcarnitine	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	3-Methylcrotonylglycine (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C5-OH-acylcarnitine (P, B)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Carnitine, esterfied (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Methylcrotonyl-CoA carboxylase (FB)	↓	↓	↓	↓	↓
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±

Table 7.5 Methylglutaconic aciduria type I

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Ataxia**	±	±	±	+	+
	Athetosis	±	±	±	±	±
	Cerebellar abnormalities	±	±	±	±	±
	Dementia	±	±	±	±	±
	Fits	±	±	±		
	Leukoencephalopathy	±	±	+	+	+
	Retardation and regression	+	+	+	+	+
	Retardation, psychomotor	±	+	+	±	±
	Seizures, febrile	±	±	±		
	Spasticity, limbs	±	±	±	±	+
Digestive	Hepatomegaly	±	±	±	±	±
	Liver dysfunction	±	±	±	±	±
Eye	Nystagmus	±	±	±	±	±
	Optic atrophy	±	±	±	±	±
Hematological	Thrombocytopenia	±	±	±		
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	ASAT/ALAT (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Creatine kinase (P)	n-↑	n-↑	n-↑		
	Glucose (P)	↓-n	↓-n	↓-n		
	Metabolic acidosis	±	±	±		

Table 7.5 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	3-Hydroxyisovaleric acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaconic acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaconyl-CoA hydratase (FB)	↓	↓	↓	↓	↓
	3-Methylglutaric acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	C5-OH-acylcarnitine (P, B)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C6-unsaturated acylcarnitine (P, B)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Carnitine, esterfied (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: cerebellar abnormalities	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
	MRS: accumulation of 3-hydroxyisovaleric acid	±	±	±	±	±
	MRS: decrease in N-acetylaspartate	±	±	±	±	±

Table 7.6 Barth syndrome

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiac arrhythmia	±	±	±	±	±
	Cardiomyopathy	+	+	+	+	+
	Cardiomyopathy, dilated	±	+	+	+	+
	Clots, stroke	±	±	±	±	±
	Heart Failure	±	±	±	±	±
	Left ventricular non-compaction	±	+	+	+	+
Dermatological	Chronic aphthous ulceration	±	±	±	±	±
Digestive	Feeding difficulties	+	+	±	±	±
	Vomiting	±	±	±	±	±
Hematological	**Neutropenia**	+	+	+	+	+
	Sepsis	±	±	±	±	±
Musculoskeletal	Exercise Intolerance	±	±	±	±	±
	Growth retardation	±	+	+	+	+
	Hypotonia, muscular	+	+	+	±	±
	Myopathy	+	+	+	+	+
Respiratory	Respiratory distress	±	±	±	±	±
Other	"Cherubic" face		±	±		
	Mild dysmorphic features	±	±	±	±	±
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Cholesterol (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Creatine kinase (P)	±	±	±	±	±
	Hypoglycemia, episodic	±	±	±	±	±
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Metabolic acidosis	±	±	±	±	±
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	2-Ethylhydracrylic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Methylglutaconic acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	3-Methylglutaric acid (U)	↑	↑	↑	↑	↑
	Abnormal cardiolipin profile	+	+	+	+	+
	Cardiolipin (tissue, FB)	↓	↓	↓	↓	↓
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	MRI: occasionally cerebral atrophy	±	±	±	±	±

Table 7.7 MEGDEL syndrome

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Basal ganglia abnormalities**	+	+	+	+	+
	Behavior difficulties	±	+	+	+	+
	Bilateral sensory hearing loss	+	+	+	+	+
	Dystonia	+	+	+	+	+
	Encephalopathy	+	+	+	+	+
	Epilepsy	±	±	±	±	±
	Extrapyramidal signs	+	+	+	+	+
	Leigh syndrome	+	+	+	±	±
	Metabolic stroke	±	+	+	+	+
	Regression, motor	±	+	+	+	+
	Retardation, psychomotor	+	+	+	+	+
	Spasticity	±	+	+	+	+
Digestive	Failure to thrive	+	+	+	±	±
	Feeding difficulties	+	+	+	±	±
Ear	Deafness, sensorineural	±	+	+	+	+
Hematological	Sepsis	+	+	+	±	±
Routine laboratory	Anion gap	+	±	+	+	+
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Lactate (CSF)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (P)	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑
Special laboratory	3-Hydroxyisovaleric acid (U)	n	n	n	n	n
	3-Methylglutaconic acid (U)	↑↑	↑↑	↑↑	↑↑	↑↑
	Filipin test	+	+	+	+	+
	MRI: bilateral hyperintensities of basal ganglia	+	+	+	+	+
	MRI: cerebral and cerebellar atrophy	+	+	+	+	+
	MRI: Leigh-like lesions	+	+	+	+	+

Table 7.8 Neonatal mitochondrial encephalocardiomyopathy

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	**Cardiomyopathy, hypertrophic**	+	+	+	+	+
	Wolf-Parkinson-White syndrome	±	±			
CNS	Apnea	±	±	±		
	Cortical-subcortical atrophy	±	±	±	±	±
	Encephalopathy	+	+	+	+	+
	Retardation, psychomotor	+	+	+	+	+
Digestive	**Failure to thrive**	+	+	+	+	
	Gastrointestinal dysmotility	±	±	±	±	±
	Hepatomegaly	+	+	±	±	±
	Liver dysfunction	±	±	±	±	±
Eye	Cataract	±	±	±	±	±
Genitourinary	Cryptorchidism	±	±	±	±	±
	Hypospadias	±	±	±	±	±
Musculoskeletal	Contractures	±	±	±	±	±
	Hypotonia, muscular	+	+	+	+	+
Renal	Renal tubulopathy	±	±	±	±	±
Respiratory	Respiratory insufficiency	±	±	±	±	±
Other	Facial dysmorphism	±	±	±	±	±

Table 7.8 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Routine laboratory	Ammonia (B)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Anion gap	+	+	+	+	+
	Creatine kinase (P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (CSF)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Lactic acidosis	+	+	±	±	±
	Metabolic acidosis	+	+	+	+	±
Special laboratory	3-Methylglutaconic acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: mild cerebellar hypoplasia	±	±	±	±	
	Pronounced ketonuria during crisis	+	+	+	+	+

Table 7.9 Costeff syndrome

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Ataxia	±	±	±	±	±
	Chorea		±	±	±	±
	Cognitive dysfunction	±	±	±	±	±
	Extrapyramidal movement disorder	±	±	±	+	+
	Mental retardation, mild		±	±	±	±
	Movement disorder, complex (Paroxysmal)	±	±	±	±	±
	Spastic paraplegia		±	±	±	±
	Spasticity	±	±	±	±	±
Eye	Nystagmus	±	+	+	+	+
	Optic atrophy	±	+	+	+	+
Special laboratory	3-Methylglutaconic acid (U)	↑	↑	↑	↑	↑
	3-Methylglutaric acid (U)	↑	↑	↑	↑	↑
	MRI: cerebral atrophy	±	±	±	±	±

Table 7.10 Methylglutaconic aciduria type IV

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy	±	±	±	±	±
CNS	Basal ganglia abnormalities	±	±	±	±	±
	Encephalopathy	±	±	±	±	±
	Intellectual disability	±	±	±	±	±
	Retardation, psychomotor	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Liver dysfunction	±	±	±	±	±
Hematological	Anemia, macrocytic	±	±	±	±	±
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	ASAT/ALAT (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Creatine kinase (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	±	±	±	±	±
	Lactate (U)	n-↑	n-↑	n-↑	n-↑	n-↑

(continued)

Table 7.10 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	3-Methylglutaconic acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaric acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Carnitine, esterfied (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Citric acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Glycogen (heart, muscle)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lipids (heart)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lipids (liver)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lipids (muscle)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine (P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±

Table 7.11 3-Hydroxy-3-methyl glutaric aciduria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy, dilated		±	±	±	±
CNS	Cerebral infarction/stroke-like encephalopathy	±	±	±	±	±
	Convulsions	+	+			
	Hypotonia, muscular	±	±	±	±	±
	Lethargy, **coma** (**during crisis**)	+	+	+	+	+
	Retardation, psychomotor	±	±	±	±	±
Digestive	Hepatomegaly	+	+	±	±	±
	Liver dysfunction	+	+	+	+	+
	Pancreatitis	±	±	±	±	±
	Vomiting, **episodic**	+	+	±	±	±
Respiratory	Respiratory distress	±	±	±	±	±
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	ASAT/ALAT (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Free fatty acids (S)	n-↑	n-↑	n-↑	n-↑	n-↑
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Hypoketotic hypoglycemia	+	+	+	+	+
	Ketones (U, P)	↓	↓	↓	↓	↓
	Lactic acidosis	+	+	+	+	+
	Metabolic acidosis	+	+	+	+	+
Special laboratory	**3-Hydroxy-3-methylglutaric acid** (**U**)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Hydroxy-3-methylglutaryl-CoA lyase (**FB**)	↓	↓	↓	↓	↓
	3-Hydroxyisovaleric acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylcrotonylglycine (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Methylglutaconic acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaric acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Adipic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	C5-OH-acylcarnitine (P, B)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C6:1 Acylcarnitine (B, P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C6DC Acylcarnitine (B, P)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Glutaric acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	MRI/CT: white matter abnormalities	±	±	±	±	±
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: occipital lesions	±	±	±	±	±
	MRS: decreased N-acetylaspartate/creatine ratio	±	±	±	±	±
	Sebacic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Suberic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑

Table 7.12 2-Methylbutyrylglycinuria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Autistic spectrum disorder	±	±	±	±	±
	Decreased cortical sulci	±	±			
	Hypotonia, muscular	±	±	±	±	±
	Retardation, psychomotor	±	±	±	±	±
Other	Patients may remain asymptomatic	±	±	±	±	±
Routine laboratory	Anion gap	±	±	±	±	±
	Glucose (P)	↓-n	↓-n	↓-n		
Special laboratory	2-Ethylhydracrylic acid (P, B)	n-↑	n-↑	n-↑	n-↑	n-↑
	2-Methylbutyric acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	2-Methylbutyrylcarnitine (P, B)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	2-Methylbutyryl-CoA dehydrogenase (FB)	↓	↓	↓	↓	↓
	2-Methylbutyrylglycine (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑

Table 7.13 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	**Cardiomyopathy**	±	+	+	±	±
CNS	Basal ganglia abnormalities	±	±	±	±	±
	Brain atrophy	±	±	±	±	±
	Choreoathetosis	±	±	±	±	±
	Dysarthria	±	±	+	+	+
	Dystonia	±	+	+	+	+
	Frontotemporal atrophy	±	±	±	±	±
	Movement disorder	±	±	±	±	±
	Retardation, psychomotor	±	+	+	+	+
	Rigidity			±	±	±
	Seizures	±	+	+	±	±
	Spasticity	±	±	±	±	±
Ear	Hearing loss, sensorineural	±	±	±	±	±
Eye	Vision, decreased	±	±	±	±	±
Other	Most patients are male	+	+	+	+	+
Routine laboratory	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	±	±	±	±	±
	Lactate (CSF)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lactic acidosis	±	+	+	±	±
	Metabolic acidosis	±	±	±	±	±
Special laboratory	**17-Beta-hydroxysteroid dehydrogenase type 10 (FB)**	↓	↓	↓	↓	↓
	2-Methyl-3-hydroxybutyric acid (U)	↑	↑	↑	↑	↑
	2-Methyl-3-hydroxy-butyrylcarnitine (P, B)	n-↑	n-↑	n-↑	n-↑	n-↑
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: frontotemporal atrophy	±	±	+	+	+
	MRI: periventricular white matter changes	±	±	±	±	±
	Tiglylcarnitine (P, B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Tiglylglycine (U)	↑	↑	↑	↑	↑

Table 7.14 Alpha-methylacetoacetic aciduria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy	±	±	±	±	±
CNS	Ataxia	±	±	±	±	±
	Basal ganglia abnormalities	±	±	±	±	±
	Brain edema	±	±	±	±	±
	Hypo or hypertonia	±	±	±	±	±
	Lethargy, **coma** (**during ketoacidotic episodes**)	±	±	±	±	±
	Movement disorder	±	±	±	±	±
	Pyramidal signs	±	±	±	±	±
	Retardation, psychomotor	±	±	±	±	±
	Seizures	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Hepatomegaly	+	+	+	±	±
	Liver dysfunction	±	+	+	±	±
	Vomiting, **episodic**	+	+	+	+	+
Hematological	Neutropenia	±	±	±	±	±
	Thrombocytopenia	±	±	±	±	±
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±
Respiratory	Respiratory distress	±	±	±	±	±
Other	Acetone-like odor to the breath	±	±			
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Anion gap	+	+	+	+	+
	Free fatty acids (S)	n	n	n		
	Glucose (P)	↓-↑	↓-↑	↓-↑	↓-↑	↓-↑
	Ketoacidosis	+	+	+	+	+
	Ketones (**U**, **P**)	↑	↑	↑	↑	↑
	Metabolic acidosis	+	+	+	+	+
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	2-Ethylhydracrylic acid (U)	↑	↑	↑	↑	↑
	2-Methyl-3-hydroxybutyric acid (**U**)	↑	↑	↑	↑	↑
	2-Methyl-3-hydroxy-butyrylcarnitine (P, B)	↑	↑	↑	↑	↑
	2-Methylacetoacetic acid (**U**)	↑	↑	↑	↑	↑
	3-Hydroxy-n-butyric acid (U, B)	↑	↑	↑		
	3-Oxothiolase activity (**FB**)	↓	↓	↓	↓	↓
	Acetoacetate (U, B)	↑	↑	↑		
	Carnitine, esterfied (P)	↑	↑	↑	↑	↑
	Carnitine, free (DBS, P)	↓	↓	↓	↓	↓
	Dicarboxylic acids (U)	n	n	n	n	n
	Glycine (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: Dentate nucleus lesions	±	±	±	±	±
	MRI: Hyperintensities (T2) of the globi pallidi	±	±	±	±	±
	MRI: signal abnormalities within the putamina	±	±	±	±	±
	MRS: Occasional increase of lactate and choline	±	±	±	±	±
	Tiglylcarnitine (P, B)	↑	↑	↑	↑	↑
	Tiglylglycine (U)	↑	↑	↑	↑	↑

Table 7.15 Isobutyryl-CoA dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	**Cardiomyopathy, dilated**	±	±	±	±	±
Digestive	Vomiting, episodic	±	±	±	±	±
Hematological	**Anemia**	±	±	±	±	±
Other	Most patients appear to be asymptomatic	±	±	±	±	±
Special laboratory	**C4-acylcarnitine**	↑	↑	↑	↑	↑
	Carnitine, esterfied (P)	↑	↑	↑	↑	↑
	Carnitine, free (DBS, P)	↓	↓	↓	↓	↓
	Isobutyryl-CoA dehydrogenase (FB)	↓	↓	↓	↓	↓
	Isobutyrylglycine (U)	↑	↑	↑	↑	↑

Table 7.16 3-Hydroxyisobutyryl-CoA deacylase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Developmental delay**	+	±	+	+	+
	Dystonia	±	±	±	±	±
	Encephalopathy acute, precipitated by infection	±	±	±	±	±
	Retardation and regression	±	±	±	±	±
	Truncal ataxia	±	±	±	±	±
Digestive	Feeding difficulties	+	+	+	+	+
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±
Other	Dysmorphism	±	±	±	±	±
Routine laboratory	Anion gap	±	±	±	±	±
	Metabolic acidosis	±	±	±	±	±
Special laboratory	2-Hydroxyisovaleric acid (U)	↑	↑	↑	↑	↑
	3-Hydroxyisobutyrylcarnitine (P, B)	↑	↑	↑	↑	↑
	Methacrylic acid conjugates (U)	↑	↑	↑	↑	↑
	MRI: abnormalities in the globus pallidus	±	±	±	±	±
	MRI: abnormalities in the midbrain	±	±	±	±	±
	MRI: agenesis of the cingulate gyrus	±	±	±	±	±
	MRI: agenesis of the corpus callosum	±	±	±	±	±
	S-2-carboxypropyl-cysteamine (U)	↑	↑	↑	↑	↑
	S-2-carboxypropyl-cysteine (U)	↑	↑	↑	↑	↑
Test	**3-Hydroxyisobutyryl-CoA deacylase (FB)**	↓	↓	↓	↓	↓

Table 7.17 3-Hydroxyisobutyrate dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Developmental delay	±	±	±	±	±
	Microcephaly	±	±	±	±	±
Digestive	**Failure to thrive**	±	+	+	±	±
Other	Dysmorphic features	±	±	±	±	±
Routine laboratory	**Ketoacidosis**	+	+	+	+	±
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Metabolic acidosis	+	+	+	+	±
Special laboratory	2-Hydroxyisovaleric acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	3-Hydroxyisobutyric acid (U)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	3-Hydroxyisobutyryl-carnitine (P, B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, esterfied (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	CT: intracerebral calcification	±	±	±	±	±
	MRI: Focal white matter lesions	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
Test	**3-hydroxyisobutyrate dehydrogenase (FB)**	↓	↓	↓	↓	↓

Table 7.18 Methylmalonate semialdehyde dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Developmental delay	±	±	±	±	±
Digestive	**Failure to thrive**	±	±	±	±	±
	Hepatomegaly	±	±	±	±	±
	Vomiting, episodic	±	±	±	±	±
Routine laboratory	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	2-Aminoisobutyrate	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Aminoisobutyric acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Hydroxyisobutyric acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Hydroxypropionic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Beta-alanine (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Ethylmalonic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methylmalonic semialdehyde dehydrogenase (FB)	↓	↓	↓	↓	↓

Table 7.19 Propionic acidemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Arrhythmia	±	±	±	±	±
	Cardiomyopathy	±	±	±	±	±
	Cardiomyopathy, dilated			±	±	±
	QT interval prolongation	±	±	±	±	±
CNS	Ataxia	±	±	±	±	±
	Basal ganglia abnormalities	±	±	±	±	±
	Brain edema	±	±	±	±	±
	Choreoathetosis	±	±	±	±	±
	Dystonia	±	±	±	±	±
	Encephalopathy acute, precipitated by infection	+	+	+	+	+
	Extrapyramidal signs	±	±	±	±	±
	Hypo or hypertonia	+	+	+	+	+
	Lethargy, coma (during ketoacidotic episodes)	+	+	+	+	+
	Metabolic stroke	±	±	±	±	±
	Retardation, psychomotor	+	+	+	+	+
	Seizures	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Feeding difficulties	+	+	+	+	+
	Hepatomegaly	+	+	±	±	±
	Liver dysfunction	±	±	±	±	±
	Pancreatitis	±	±	±	±	±
	Vomiting	±	±	±	±	±
Ear	Hearing loss, sensorineural	±	±	±	±	±
Endocrine	Decreased body height	±	±	±	±	±
	Hypogonadism (in females), hypergonadotropic				±	±
Eye	Optic atrophy	±	±	±	±	±
Hematological	Anemia	+	+	+	+	+
	Myelodysplasia	±	±	±	±	±
	Neutropenia	+	+	+	+	+
	Thrombocytopenia	+	+	+	+	+
Musculoskeletal	**Hypotonia, muscular**	+	+	+	±	±
	Osteopenia		±	±	±	±
Renal	Renal failure, chronic					±
	Temporary impairment of renal function	±	±	±	±	±

Table 7.19 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Respiratory	Respiratory insufficiency	±	±	±	±	±
Other	Low body temperature during crisis	±	±	±		
Routine laboratory	Ammonia (B)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Anion gap	+	+	+	+	+
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Hyperglycemia	±	±			
	Ketoacidosis	+	+	+	+	+
	Ketones (U, P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lactate (U)	↑	↑	↑	↑	↑
	Metabolic acidosis	+	+	+	+	+
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	**3-Hydroxypropionic acid (U)**	↑	↑	↑	↑	↑
	Carnitine, esterfied (P)	↑	↑	↑	↑	↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glutamine (CSF)	n-↑	n-↑	n-↑	n-↑	n-↑
	Glutamine (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glycine (P, U, CSF)	↑	↑	↑	↑	↑
	Methylcitric acid (U)	↑	↑	↑	↑	↑
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: delayed myelination	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
	MRS: decrease in N-acetylaspartate	±	±	±	±	±
	MRS: elevated lactate	±	±	±	±	±
	MRS: elevation of glutamine/glutamate	±	±	±	±	±
	Propionylcarnitine (P, B)	↑	↑	↑	↑	↑
	Propionyl-CoA carboxylase activity (WBC, FB)	↓	↓	↓	↓	↓
	Propionylglycine (U)	↑	↑	↑	↑	↑
	Tiglylglycine (U)	↑	↑	↑	↑	↑

Table 7.20 Methylmalonic acidemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy	±	±	±	±	±
CNS	Ataxia	±	±	±	±	±
	Basal ganglia abnormalities	±	±	±	±	±
	Brain edema	±	±	±	±	±
	Choreoathetosis	±	±	±	±	±
	Dystonia	±	±	±	±	±
	Encephalopathy acute, precipitated by infection	+	+	+	+	+
	Extrapyramidal signs	±	±	±	±	±
	Hypo or hypertonia	±	±	±	±	±
	Lethargy, coma (during ketoacidotic episodes)	+	+	+	+	+
	Metabolic stroke	±	±	±	±	±
	Retardation, psychomotor	+	+	+	+	+
	Seizures	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Feeding difficulties	+	+	+	+	+
	Hepatomegaly	+	+	±	±	±
	Liver dysfunction	±	±	±	±	±
	Pancreatitis	±	±	±	±	±
	Vomiting	±	±	±	±	±

(continued)

Table 7.20 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Endocrine	Decreased body height	±	±	±	±	±
Eye	Optic neuropathy	±	±	±	±	±
Hematological	Anemia	+	+	+	+	+
	Neutropenia	+	+	+	+	+
	Thrombocytopenia	+	+	+	+	+
Musculoskeletal	**Hypotonia, muscular**	+	+	+	±	±
	Osteopenia		±	±	±	±
Renal	**Progressive renal impairment**	±	+	+	+	+
	Reduced glomerular filtration rate	±	±	+	+	+
	Renal tubulopathy	±	±	±	±	±
	Tubulointerstitial nephritis	±	±	±	±	±
Respiratory	Respiratory insufficiency	±	±	±	±	±
Other	Hypothermia during crisis	±	±	±		
Routine laboratory	Ammonia (B)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Anion gap	+	+	+	+	+
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Hyperglycemia	±	±			
	Ketoacidosis	+	+	+	+	+
	Ketones (U, P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lactate (U)	↑	↑	↑	↑	↑
	Metabolic acidosis	+	+	+	+	+
	Uric acid (P)	n-↑	n-↑	n-↑	n-↑	n-↑
Special laboratory	14C-Propionate incorporation assay (FB)	↓	↓	↓	↓	↓
	3-Hydroxypropionic acid (U)	↑	↑	↑	↑	↑
	Carnitine, esterfied (P)	↑	↑	↑	↑	↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glutamine (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glycine (P, U)	↑	↑	↑	↑	↑
	Methylcitric acid (U)	↑	↑	↑	↑	↑
	Methylmalonic acid (P, U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Methylmalonylcarnitine (P, B)	↑	↑	↑	↑	↑
	Methylmalonyl-CoA mutase activity (FB)	↓	↓	↓	↓	↓
	MRI: basal ganglia lesions	±	±	±	±	±
	MRI: cerebral atrophy	±	±	±	±	±
	MRI: delayed myelination	±	±	±	±	±
	MRI: white matter changes	±	±	±	±	±
	MRS: decrease in N-acetylaspartate	±	±	±	±	±
	MRS: elevated lactate	±	±	±	±	±
	Propionylcarnitine (P, B)	↑	↑	↑	↑	↑

Table 7.21 Malonic aciduria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	**Cardiomyopathy**	±	+	+	+	+
CNS	**Developmental delay**	±	+	+	±	±
	Dystonia	±	±	±	±	±
	Encephalopathy acute, precipitated by infection	±	±	±	±	±
	Epilepsy	±	±	±	±	±
Digestive	Hepatomegaly	+	+	±	±	±
	Vomiting	+	+	+	±	±
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±

Table 7.21 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Routine laboratory	Ammonia (B)	n-↑	n-↑	n-↑	n-↑	n-↑
	Base excess	±	±	±	±	±
	Cholesterol (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketones (U, P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Metabolic acidosis	±	±	±	±	±
Special laboratory	3-Hydroxybutyric acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Adipic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ethylmalonic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Fumaric acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Glutaric acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Malic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Malonic acid (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Malonylcarnitine	↑	↑	↑	↑	↑
	Methylmalonic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	MRI/CT: Frontotemporal atrophy	±	±	±	±	±
	MRI/CT: white matter abnormalities	±	±	±	±	±
	MRI: basal ganglia lesions	±	±	±	±	±
	Sebacic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Suberic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Succinic acid (U)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Urine MMA/MA ratio	↓	↓	↓	↓	↓
Test	**Malonyl-CoA decarboxylase activity**	↓	↓	↓	↓	↓

Table 7.22 Combined MMA and MA

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Cardiomyopathy	±	±	±	±	±
CNS	Autistic spectrum disorder	±	±	±	±	±
	Coma, lethargy	±	±	±	±	±
	Developmental delay	±	+	+	±	±
	Dystonia	±	±	±	±	±
	Loss of speech		±	±	±	±
	Memory problems		±	±	±	±
	Microcephaly	±	±	±		
	Migraine, ocular			±	±	±
	Seizures	±	±	±	±	±
Digestive	Failure to thrive	±	±	±	±	±
	Feeding difficulties	±	±	±	±	±
	Liver dysfunction	±	±	±	±	±
	Vomiting	±	±	±	±	±
Musculoskeletal	Hypotonia, muscular	±	±	±	±	±
Other	Mild dysmorphic features	±	±	±	±	±
Routine laboratory	Base excess	±	±	±	±	±
	Cholesterol (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Glucose (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Ketoacidosis	±	±	±	±	±
	Lactate (P)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Metabolic acidosis	±	±	±	±	±

(continued)

Table 7.22 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Carnitine, free (DBS, P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Malonic acid (**U**)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Malonylcarnitine	↑	↑	↑	↑	↑
	Methylmalonic acid (**P**, **U**)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	MRI: hyperintensities (T2)	±	±	±	±	±
	Propionylcarnitine (P, B)	n	n	n	n	n
	Urine MMA/MA ratio	↑	↑	↑	↑	↑

7.5 Reference Values

Urine/spot tests

	2,4-Dinitrophenylhydrazine (DNPH) test	Ferric chloride test
Normal	No precipitate	No color change

Plasma quantitative amino acids (μmol/l) (Ion exchange column chromatography or high-performance liquid chromatography, HPLC)

Age	Valine	Isoleucine	Leucine	Alloisoleucine
Newborn[a]	86–220	23–102	48–180	0
Child	64–320	30–105	59–180	0
Adult	99–286	30–108	61–162	0

Age	Glycine	Methionine	Threonine
Newborn[a]	220–500	6–46	60–200
Child	130–400	9–45	60–200
Adult	120–550	9–59	43–130

[a]The national standards and local reference ranges for newborn screening or selective screening tests should be used

Organic acids in urine (mmol/mol creatinine), blood plasma or serum (µmol/l), or dried blood spots (DBS, µmol/l) (gas chromatography/mass spectrometry, GC/MS)

Age	Urine 2-oxoiso-caproic acid	Urine 2-oxo-3-methyl-valeric acid	Urine 2-oxoiso-valeric acid	Urine 2-hydroxyisovaleric acid	Urine 2-hydroxy-isocaproic acid	Urine 2-hydroxy-3-methyl-valeric acid	Urine lactate	Venous blood lactate (mmol/l)
All	<2	<2	<2	<2	<2	<2	<197	<2.2

Age	Plasma/serum isovaleric acid	DBS isovalerylglycine	Urine isovalery-glycine	Urine 3-hydroxyisovaleric acid	Urine 4-hydroxyisovaleric acid	Urine isovalerylglucuronide	Urine 3-methyl-crotonyl-glycine	Urine 3-methylglutaconic acid	Urine 3-methyl-glutaric acid	Urine 3-hydroxy-3-methylglutaric acid
All	<10	<0.5	<10	<16	<2	ND	<2	<6	<7	<36

Age	Urine 3-hydroxypropionate	DBS 3-hydroxypropionate	Urine methyl-citrate	Urine propionyl-glycine	Urine 2-methyl butyrylglycine	Urine methylmalonate	DBS methylmalonate	Urine 2-methyl-3-hydroxybutyrate	Urine 3-hydroxyisobutyrate	Urine 2-methyl-acetoacetate
All	<2	ND	<2	<2	<2	<2	<0.4	<12	<24	<2

Age	Urine 2-methylbutyrylglycine	Urine 2-ethylhydracrylic acid	Urine 2-methyl-3-hydroxybutyrate	Urine tiglylglycine	Urine isobutyrylglycine	Urine S-2-carboxypropyl-cysteamine and S-2-carboxypropyl-cysteine	Urine 3-hydroxyisobutyrate
All	<2	<2	<11	<2	<3.8	ND	<33

Age	Urine 3-hydroxypropionate	DBS 3-hydroxypropionate	Urine methyl-citrate	Urine tiglylglycine	Urine propionylglycine	Urine methylmalonate	DBS methylmalonate	Plasma/serum methylmalonate	Urine malonic acid
All	<10	ND	<8	<2	<2	<2	<0.4	<0.2	<5

Acylcarnitines in dried blood spots (DBS, µmol/l) (tandem mass spectrometry)

Age	Free carnitine (C0)	C3-/propionyl-carnitine	C3-DC/malonylcarnitine	C4-/butyrylcarnitine + isobutyrylcarnitine	C4-DC-/methylmalonyl carnitine	C4-OH-/3-OH-isobutyrylcarnitine	C5-/isovaleryl-/2-methylbutyryl carnitine	C5:1-/pentenoyl-/tiglylcarnitine	C5-OH-/3-hydroxyisovaleryl-/2-methyl-3-OH-butyrylcarnitine
All[a]	10–60	<3.60	<0.20	<0.50	<0.54	<0.39	<0.20	<0.03	<0.36

The national standards and local reference ranges for newborn screening or selective screening tests should be used

[a]Of note, acylcarnitine reference values are age dependent (see special literature)

7.6 Pathological Values

Urine/spot tests

Disorder	2,4-Dinitrophenylhydrazine (DNPH) test[a]	Ferric chloride test[a]
7.2 Maple syrup disease (MSUD)	Yellow precipitate	Greenish-gray color

[a]This test has historical importance but has since been replaced (e.g., through newborn screening or selective metabolic screening using tandem mass spectrometry)

Plasma quantitative amino acids (μmol/l) (ion exchange column chromatography or high-performance liquid chromatography, HPLC)

Disorder	Valine	Isoleucine	Leucine	Alloisoleucine	% normal activity of BCKD[a] complex
7.1. BCAT deficiency	220–1,500	Increased	Increased	–	Normal
7.2 MSUD					
Clinical forms:					
Classic	To 7,550	To 4,800	To 10,800	≥5–970	0–2
Intermediate[b]	To 1,000	To 1,000	To 2,000	2–220	3–30
Intermittent[b]	To 1,000	To 1,000	To 4,000	2–220	3–30
Thiamin responsive	To 1,000	To 1,000	To 5,000	Present	2–40

[a]*BCKD* Branched-chain α-keto acid dehydrogenase
[b]Levels may only be abnormal during acute episodes of ketoacidosis in the intermittent/intermediate form

Comments/Additions

1. Leucine, isoleucine, and valine are usually not elevated in metabolic defects distal from the BCKD complex as this complex catalyzes an irreversible enzymic reaction.
2. Secondary findings, such as elevated plasma glycine and alanine concentrations, are not listed separately.

Organic acids in urine (mmol/mol creatinine), blood plasma or serum (μmol/l), or dried blood spots (DBS, μmol/l) (gas chromatography/mass spectrometry, GC/MS)

Disorder abbreviation	Urine 2-oxoiso-caproic acid	Urine 2-oxo-3-methyl-valeric acid	Urine 2-oxoiso-valeric acid	Urine 2-hydroxy-isovaleric acid	Urine 2-hydroxy-isocaproic acid	Urine 2-hydroxy-3-methyl-valeric acid	Urine lactate[a]	Venous blood lactate (mmol/l)[a]
7.1 BCAA transferase deficiency	–	–	–	–	–	–		
7.2 MSUD	To 4,400	To 2,500	To 800	To 3,600	To 80	To 400	n-↑	n-↑

Disorder abbreviation	Plasma/serum isovaleric acid	DBS isovalerylglycine	Urine isovalerylglycine	Urine 3-hydroxy-isovaleric acid	Urine 4-hydroxy-isovaleric acid	Urine isovalerylglucuronide	Urine 3-methyl-crotonyl-glycine
7.3 IVA	600–5,000 (with episodes); 10–50 (between episodes)	1.3–80.0	To 4,980	To 2,000	20–300	Detectable[b]	–
7.4 MCCD	–	–	–	96–8,850	–	–	40–4,042

Disorder abbreviation	Urine 3-hydroxy-isovaleric acid	Urine 3-methyl-crotonyl-glycine	Urine 3-methylglutaconic acid	Urine 3-methylglutaric acid	Urine 3-hydroxy-3-methylglutaric acid
7.5 MGA1	47–3,840	–	168–2,900	4.5–9.0	–
7.6 Barth syndrome	–	–	18–600	10–85	–
7.7 MEGDEL syndrome	–		16–196	n-↑	
7.8 Neonatal mitochondrial encephalocardiomyopathy	–		12–361	n-↑	
7.9 Costeff syndrome	–	–	9–187 (combined excretion with 3-methylglutaric acid)	–	
7.10 MGA4	–	–	23–1,793	5–215	–
7.11 HMG-CoA lyase deficiency	60–9,600	0–400	140–24,200	14–3,000	200–11,000

Disorder abbreviation	Urine 2-methylbutyrylglycine	Urine 2-ethylhydracrylic acid	Urine 2-methyl-3-hydroxybutyrate	Urine tiglylglycine	Urine 2-methyl-acetoacetate	Urine isobutyrylglycine	Urine S-2-carboxypropyl-cysteamine + S-2-carboxypropyl-cysteine	Urine 3-hydroxy-isobutyrate
7.12 MBD deficiency	3–37	↑	–			–	–	
7.13 MHBD deficiency	–	n-↑	11–30	↑		–	–	
7.14 BKT deficiency	–		11–4,400	2–1,000	2–650	–	–	
7.15 IBD deficiency	–	–	–	–		↑	–	
7.16 HIBCH deficiency	–	–					↑	
7. 17 HIBADH deficiency	–	–						60–600 (between episodes); up to 10,000 (with episodes)

Disorder abbreviation	Urine 3-hydroxypropionate	DBS 3-hydroxypropionate	Urine methyl-citrate	Urine tiglylglycine	Urine propionyl-glycine	Urine methylmalonate	Plasma/(DBS) methylmalonate	Urine malonic acid
7.18 MMSDH deficiency[c]	n-↑	n-↑				n (-↑)	n (-↑)	
7.19 PA	20–2,000	69–107	150–2,800	13–497	2–450	–	–	
7.20 MMA	4–1,000	11–32	To 2,800	(↑)	(↑)	20–16,543	24–6,129 (2–2,920)	–
7.21 MA						17–210	n-↑	100–5,440
7.22 CMAMMA						21–1,830	0.4–48	3–600

Levels may only be abnormal in variant forms during metabolic decompensation. Range of (but not all) metabolites are given

[a]As an elevated concentration of lactate is a frequent finding, lactate is therefore not listed repeatedly

[b]Isovalerylglucuronide is more likely to be excreted when the concentration of 3-hydroxyisovaleric acid is high

[c]3-Hydroxy-/3-aminoisobutyric acids, 2-aminoisobutyrate, 3-hydroxypropionic acids, and ethylmalonate may also be increased in methylmalonate semialdehyde dehydrogenase deficiency

Acylcarnitines in dried blood spots (DBS, µmol/l) (tandem mass spectrometry)

Disorder abbreviation	Free carnitine (C0)	C3-/ propionyl-carnitine	C4-/ butyrylcarnitine + isobutyrylcarnitine	C3-DC/ malonylcarnitine	C4-DC-/ methylmalonyl carnitine	C4-OH-/3-OH-isobutyrylcarnitine	C5-/ isovaleryl-/2-methylbutyryl carnitine	C5:1-/ pentenoyl-/ tiglylcarnitine	C5-OH-/3-hydroxyisovaleryl-/2-methyl-3-OH-butyrylcarnitine
7.1 BCAA transferase deficiency	n								
7.2 MSUD	n								
7.3 IVA	↓-n						↑		
7.4 MCCD	↓-n								↑
7.5 MGA1	↓-n								↑
7.6 Barth syndrome	↓-n								n-(↑)
7.7 MEGDEL syndrome	?								
7.8 Neonatal mitochondrial encephalocardiomyopathy	?								
7.9 Costeff syndrome	(n)								n-(↑)
7.10 MGA4	↓-n								n-(↑)
7.11 HMG CoA lyase deficiency	↓-n								↑
7.12 MBD deficiency	↓-n						↑		
7.13 MHBD deficiency	↓-n							↑	↑
7.14 BKT deficiency	↓-n							↑	↑
7.15 IBD deficiency	↓-n		↑						
7.16 HIBCH deficiency	↓-n					↑			
7.17 HIBADH deficiency	↓-n					↑			
7.18 MMSDH deficiency	(n)								
7.19 PA[a]	↓-n	↑							
7.20 MMA[a]	↓-n	↑			↑				
7.21 MA	↓-n			↑					
7.22 CMAMMA	↓-n	n		↑					

Levels may only be abnormal in patients with variant forms during metabolic decompensation
Acylcarnitine concentration may increase following L-carnitine supplementation
[a]Molar ratios should be applied for diagnostic purposes, e.g., C3/acetylcarnitine (C2) and C3/C0

7.7 Diagnostic Flow Chart

A positive newborn screening test for leucine should be confirmed by quantitative plasma amino acid analysis and is usually only seen in MSUD. High-risk newborns require an early newborn screening, e.g., at day 1 along with preventative dietary intervention. Abnormal blood acylcarnitine species may be seen in the other disorders in this pathway, and making the correct diagnosis depends on the analysis of urinary organic acids by combined GC-MS. Further diagnostic information is obtained through analysis of urinary acylglycines and (in selected instances) intact fibroblast oxidation studies or direct enzyme analyses. Essentially, the detection of unusual body odor (maple syrup, sweaty feet), acidosis, ketosis, elevated ammonia, hypoglycemia, or carnitine deficiency suggests that urine organic acid analysis should be performed. Patients with many of these disorders may be asymptomatic at birth and are identified only on the basis of an abnormal newborn screening using tandem mass spectrometry. In patients not screened as newborns, nonspecific symptoms such as failure to thrive or developmental delay should trigger a metabolic evaluation that may identify a diagnostic metabolite. Blood acylcarnitines and urinary organic acid profiling are again essential for the correct differential diagnosis followed by confirmatory analysis. The disorders of isoleucine and valine metabolism are also detected in a sequential process that begins with the evaluation of the symptoms and signs displayed by the patient (selective metabolic screening) or in some countries on newborn screening. Clinical chemistry is helpful in the assessment of ketogenesis by urinary tests for ketone bodies or quantification of 3-hydroxybutyrate and acetoacetate in the blood. The electrolytes, blood gases, and pH provide evidence of acidosis, and it is important to test for hyperammonemia. Analysis of plasma amino acids and blood acylcarnitines is helpful. In virtually all instances, the definitive diagnosis will come from organic acid analysis of the urine, followed by further enzymatic or molecular tests.

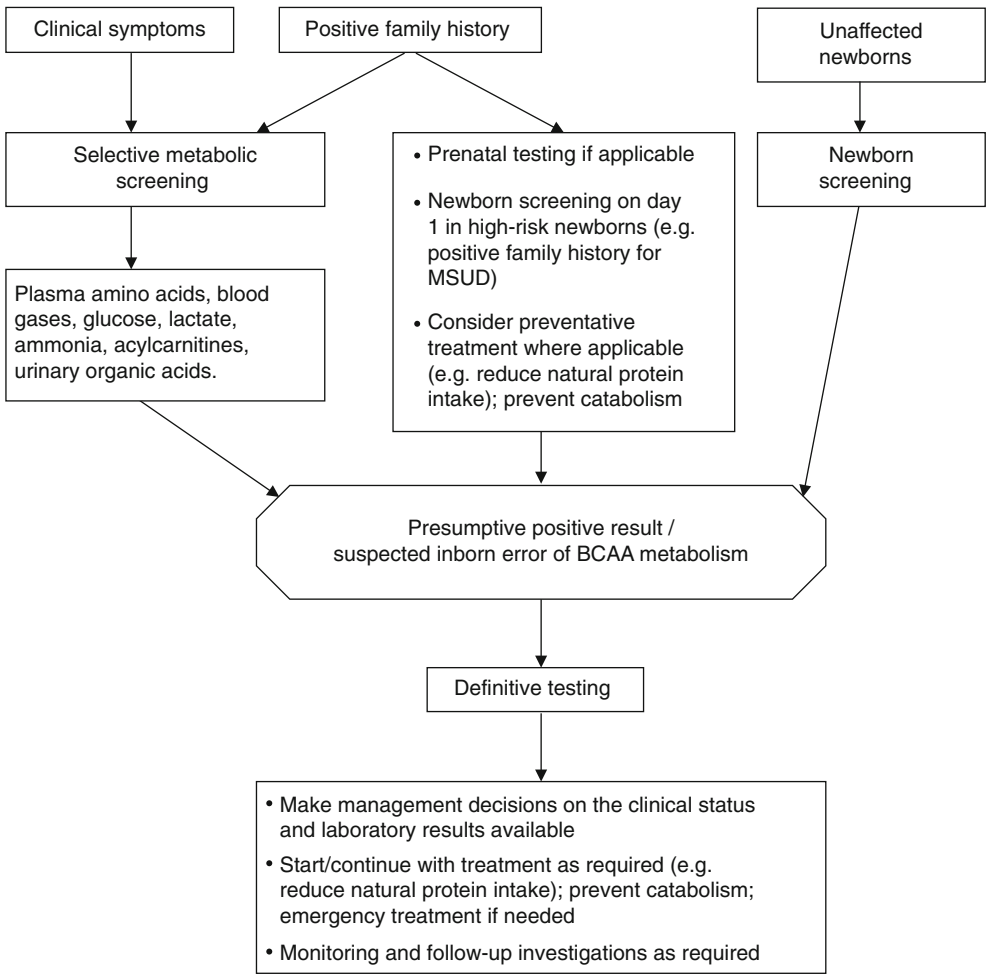

Fig. 7.2 Diagnostic flow chart

7.8 Specimen Collection, Prenatal Diagnosis and DNA Analysis

7.8.1 Specimen Collection

Tests	Sample requirements
Urine	5–10 ml, random, fresh or frozen without preservatives and shipped frozen (packed in dry-ice) or lyophilized and shipped at room temperature with original volume specified or shipped as fresh sample with 1–2 drops of chloroform for preservation Test urinary amino acids e.g. in patients with hyperammonemia or kidney dysfunction, otherwise plasma sample preferred
Amino acids	
Organic acids	
Carnitine (free/total)	
Acylglycines	
2,4-dinitrophenylhydrazine (DNPH) test	Fresh or frozen random This test has historical importance but has since been replaced May give false negative results Usually positive if blood leucine is greater than 800 µmol/l May be positive in other conditions with oxoacids False positives with methenamine and radio-opaque contrast material
Ferric chloride test	Fresh or frozen random This test has historical importance but has since been replaced Turned colors to various abnormal urinary metabolites
Plasma	Plasma, 0.5–1.0 ml for each determination from heparinized or EDTA blood (or serum) supernatant from clinical centrifugation (within 20 min), fresh or promptly frozen and shipped frozen (packed with dry-ice) or lyophilized and shipped at room temperature with original volume specified. For quantitative amino acids: random or semi-fasting conditions (i.e. 4 h) Plasma ketone body concentration changes with fasting over time, check glucose simultaneously
Amino acids	
Organic acids	
Carnitine (free/total)	
Acylcarnitine profile	
Organic acids (such as methylmalonic acid) ketone bodies	
Dried blood spots	Drops of whole blood correctly collected on filter paper It is important neither to overload nor to dilute the sample Blood spots should dry completely before storage or transportation (at room temperature)
Acylcarnitine profile	
Amino acids	
Organic acids (such as methylmalonic acid)	
Cerebrospinal fluid	0.5–1 ml for each investigation (standard plastic lumbar puncture tube), fresh or frozen and shipped frozen (packed with dry-ice). Check plasma amino acids simultaneously
Amino acids	

7.8.2 Prenatal Diagnosis

Disorder		Material[a]	Timing, trimester
7.1	BCAA aminotransferase deficiency	?	
7.2	Maple syrup disease	Molecular analysis,	I, II
		CV tissue, cultured AFC	
7.3	Isovaleric acidemia	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.4	Isolated 3-methylcrotonyl-CoA carboxylase deficiency	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.5	3-Methylglutaconic aciduria type I (3-methylglutaconyl-CoA hydratase deficiency)	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.6	3-Methylglutaconic aciduria type II (Barth syndrome)	Molecular analysis	I, II
7.7	MEGDEL syndrome	Molecular analysis	I, II
7.8	Neonatal mitochondrial encephalocardiomyopathy[a]	Molecular analysis	I, II
7.9	3-Methylglutaconic aciduria type III (Costeff syndrome)[a]	Molecular analysis	I, II
7.10	3-Methylglutaconic aciduria type IV[b]	?	
7.11	3-Hydroxy-3-methylglutaric aciduria	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.12	2-Methylbutyrylglycinuria	Molecular analysis	I, II

Disorder		Material[a]	Timing, trimester
7.13	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency	Molecular analysis	I, II
7.14	Beta-ketothiolase deficiency	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.15	Isobutyryl CoA dehydrogenase deficiency	Molecular analysis,	I, II
		CV tissue, cultured AFC	
7.16	3-Hydroxyisobutyryl-CoA deacylase	Molecular analysis deficiency	I, II
7.17	3-Hydroxyisobutyrate dehydrogenase deficiency[b]	Molecular analysis	I, II
		Amniotic fluid	II
7.18	Methylmalonate semialdehyde dehydrogenase deficiency[b]	Molecular analysis	I, II
7.19	Propionic acidemia	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.20	Methylmalonic academia	Molecular analysis,	I, II
		CV tissue, cultured AFC,	
		Amniotic fluid	II
7.21	Malonic aciduria	Molecular analysis,	I, II
		CV tissue, cultured AFC	
		Amniotic fluid	II
7.22	Combined methylmalonic and malonic aciduria[b]	Molecular analysis	I, II
		Amniotic fluid	II

[a]Prenatal diagnostic tests comprise of direct mutation analysis using chorionic villus samples/amniocytes, enzyme testing in chorionic villus (CV) tissue or cultured amniocytes, and metabolite analyses in amniotic fluid. Contact specialized laboratory for details
[b]Thus far, studies have been limited to patients categorized according to confirmatory enzymatic/molecular test results

7.8.3 DNA Analysis

Disorder		Material	Methodology
7.1	BCAA aminotransferase deficiency	*For all entities*: WBC, FB or other suitable cells or tissue samples may be used	*For all entities*: RT-PCR, reverse transcription-polymerase chain reaction/genomic amplification and sequencing In some cases allele-specific oligonucleotide hybridization or single-stranded conformational polymorphism analysis may be used
7.2	Maple syrup disease		
7.3	Isovaleric acidemia		
7.4	Isolated 3-methylcrotonyl-CoA carboxylase deficiency		
7.5	3-Methylglutaconic aciduria type I (3-methylglutaconyl-CoA hydratase deficiency)		
7.6	3-Methylglutaconic aciduria type II (Barth syndrome)		
7.7	MEGDEL syndrome		
7.8	Neonatal mitochondrial Encephalomyopathy		
7.9	3-Methylglutaconic aciduria type III (Costeff syndrome)		
7.10	3-Methylglutaconic aciduria type IV[a, b]		
7.11	3-Hydroxy-3-methylglutaric aciduria		
7.12	2-Methylbutyrylglycinuria		
7.13	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency		
7.14	Beta-ketothiolase deficiency		
7.15	Isobutyryl CoA dehydrogenase deficiency		
7.16	3-Hydroxyisobutyryl-CoA deacylase deficiency		
7.17	3-Hydroxyisobutyrate dehydrogenase deficiency[b]		
7.18	Methylmalonate semialdehyde dehydrogenase deficiency[b]		
7.19	Propionic acidemia		
7.20	Methylmalonic academia		
7.21	Malonic aciduria		
7.22	Combined methylmalonic and malonic aciduria[b]		

[a]Very limited evidence
[b]Thus far, studies have been limited to patients categorized according to confirmatory enzymatic/molecular test results

7.9 Treatment Summary

The mainstay of treatment for all of the disorders is to limit intake of the affected amino acid(s) while preventing catabolism. With severe forms of the disorders, special medical foods (devoid of all BCAA, Leu, Ile, Val or Ile/Met/Thr/Val, as required for the different conditions) are needed to allow for adequate caloric, protein, and other nutrient intake. Milder forms may only require a moderately reduced natural protein intake. The amount of natural whole protein tolerated is determined by monitoring parameters such as growth, control of acidosis, excretion of abnormal metabolites, blood amino acid levels, and testing for body protein stores. The least restrictive dietary approach should be taken in order to avoid over-treatment and nutritional deficiencies. Emergency treatment includes promotion of anabolism using a special high-calorie diet, transient stop of natural protein intake or of the precursor amino acids, carefully adjusted IV treatment including adequate amounts of IV dextrose, correction of acidosis, detoxification, prevention of brain edema, and emergency hemodialysis in case of coma/encephalopathy with severe hyperammonemia or profound metabolic acidosis in classic forms of the disorders. Carnitine is used in a quantity of conditions to support excretion of organic acids as carnitine adducts, thus sparing coenzyme-A and preserving the function of the Krebs cycle. Hyperammonemia may occur, particularly in PA and MMA, but conjugating agents are typically not indicated for therapy as ammonia normalizes with reversal of the primary metabolic derangement. If severe, hemodialysis may be indicated. The chronic treatment of severe forms of the disorders, particularly of PA and MMA, is also challenging. Late complications must be anticipated, including neurologic complications, renal failure (particularly in MMA), or cardiomyopathy. Liver transplantation and combined liver/kidney transplantation have been applied in a number of cases and there is evidence of benefit, but concerns arise because of documented cases of neurologic complications (e.g., in MMA).

Emergency Treatment

- **Disorder 7.1: Branched-Chain Amino Acid Transferase Deficiency**
  - Management may be adapted from tables for disorder **7.2** (MSUD). Follow-up treatment relies on the correct diagnosis.
- **Disorder 7.2: Maple Syrup Urine Disease**

Emergency treatment (includes management of ill neonates) for disorder 7.2

Objective	Treatment
1. Correct dehydration	Normal saline bolus as clinically indicated. Start IV dextrose 10–12.5 % at 1–1.5 times maintenance; add NaCl and KCl depending on renal output and serum electrolyte levels. Plan rehydration over a 48 h period to prevent cerebral edema
2. Correct acidosis	Usually corrects with reestablishment of anabolic state. In extremis, give 1–2 mEq/kg of NaBicarbonate
3. Maintain normal plasma sodium and osmolality levels. High risk for SIADH	(a) Check plasma sodium (aim for 140–145 mEq/l with minimal fluctuation) and plasma osmolality (290–300 mosm/l) regularly; monitor intake and output, body weight; urine osmolality (≤300–400 mosm/l), urine electrolytes and output (2–4 ml/kg/h) (b) Give 3 % NaCl, dosage carefully calculated to replace deficit if hyponatremic. May also need furosemide 0.50 (0.25–1) mg/kg per dose every 6–8 h if plasma osmolality falls (c) Limit free water intake observe for fluid overload due to excessive vasopressin production (d) Monitor for signs of increased intracranial pressure
4. Correct hyperglycemia (blood glucose >200 mg/dl) induced by IV fluids	Regular insulin drip, e.g., 0.05–0.1 units/kg/h until blood glucose is controlled
5. Reestablish anabolism	(a) BCAA-free formula or IV fluids to provide total caloric intake of 120–150 % of maintenance or give step 1 sick-day diet by PO or NG/G-tube (see table protocol for intercurrent illness below)[a] (b) Add interlipid 2–3 g/kg/day if NPO (c) Add back natural protein beginning with e.g., 100 mg of leucine per day after 24 h; total protein including BCAA-free supplements 2.5–3.5 g/kg/day
6. Reduce persistently elevated leucine levels or hyperammonemia or encephalopathy	(a) Hemodialysis (HD) or hemofiltration (HF) in encephalopathic patients if intensified treatment (measure 1–6) is insufficient over a period of 2–4 h (b) Expect rate of decrease in plasma leucine levels >750 μmol/l per 24 h

[a]Isoleucine and valine levels should be high during crisis, at over 400–600 μM, to suppress entry of leucine into the brain. Isoleucine and valine usually need to be added early (after 24 h) into treatment (e.g., 40–100 mg/kg/day each). Leucine is reintroduced when its plasma level falls close to the normal range (e.g., total daily dose of 100 mg of leucine per day when plasma level below 400 μmol/l, 200 mg/day when level below 300 μmol/l; provide in total 2.5–3.5 g/kg/day of protein equivalent). Aim at target ratios of approximately 1:2:2 for plasma leucine, isoleucine, and valine, respectively

Comments/Additions

1. Stop all natural protein sources initially but add back leucine restricted source after 24 h to reestablish protein anabolism.
2. Monitor laboratory studies including blood glucose, electrolytes, pH, blood gases, ammonia, lactate, osmolality, plasma amino acids, urinary organic acids, and dipstick for ketones as indicated by the clinical history and examination. Acute pancreatitis may accompany metabolic crisis.
3. Patients with the E3 subunit deficiency may experience severe lactic acidosis and abnormal blood glucose.
4. Thiamine 10 mg/kg/day (50–500 mg/day) may be given until genotype is known.

Protocol for intercurrent illness for disorder 7.2

Treatment	Branched-chain amino acid-free special medical food	Natural food leucine intake
First 24 h	1.2–1.5 times usual daily amount with additional isoleucine and valine[a]	None
24–48 h	1.2–1.5 times usual daily amount with additional isoleucine and valine[a]	None to half usual dietary intake
>48 h or when well	Usual daily amount	Gradual increase to usual full dietary intake

[a]Additions of isoleucine and valine should be increased during sick days. Goal is to keep levels of isoleucine and valine between 150–350 and 200–400 μM, respectively, when the patient is well and at over 400–600 μM when ill

Comments/Additions

1. 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.
2. If the patient is unable to take in oral fluids and has persistent vomiting or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

Disorder 7.3: Isovaleric Acidemia
Disorder 7.4: 3-Methylcrotonylglycinuria[1]
Disorder 7.5: 3-Methylglutaconic Aciduria type I[2]
Disorder 7.11: 3-Hydroxy-3-Methylglutaric Aciduria[3]

[1]Most patients do not become acutely ill.

[2]Treatment is mainly symptomatic.

[3]Patients with HMGCL (disorder **7.11**) usually present with acute hypoketotic or nonketotic hypoglycemia, and dehydration may be underestimated. Give IV glucose bolus (e.g., 2 ml/kg of dextrose 10 %) in a hypoglycemic patient. Add carnitine (e.g., 100 mg/kg/day) (Dasouki et al. 1987).

Emergency treatment (includes management of ill neonates) for disorders 7.3, 7.4, 7.5, and 7.11

Objective	Treatment
1. Treat dehydration	Normal saline bolus as clinically indicated. Start IV dextrose 10–12.5 % at 1–1.5 times maintenance; add NaCl and KCl depending on renal output and serum electrolyte levels
2. Correct acidosis	Usually corrects with reestablishment of anabolic state. In extremis, give 1–2 mEq/kg of NaBicarbonate
3. Correct hyperglycemia (blood glucose >200 mg/dl) induced by IV fluids	Regular insulin drip, e.g., 0.05 units/kg/h, until blood glucose is controlled
4. Reestablish anabolism	(a) Leucine-free formula or IV fluids (plus low fat in HMGCL deficiency/disorder **7.11**) with caloric intake 120–150 % of maintenance (b) Can add intralipids for additional calories except for HMGCL deficiency (disorder **7.11**)
5. Metabolite conjugation	Carnitine: 100 mg/kg/day in three divided doses IV or PO Glycine (IVA only): usual daily dose (e.g., 250 mg/kg/day) in sick-day enteral formula or TPN

Comments/Additions

1. Stop all natural protein sources initially. Begin to add back leucine-restricted protein after 24 h and complete protein after 48 h.
2. Monitor laboratory studies including blood glucose, electrolytes, pH, blood gases, ammonia, lactate, plasma amino acids, urinary organic acids, acylcarnitine profile, liver function tests, CK, and any other laboratory tests indicated by the clinical history and examination.

Protocol for intercurrent illness: initial measures for disorders 7.3, 7.4, 7.5, 7.11

Treatment	Leucine-free special medical food[a]	Natural food leucine intake	L-carnitine (mg/kg/day)
First 24 h	1.2–1.5 times usual daily amount	None	100
24–48 h	1.2–1.5 times usual daily amount	None to half usual dietary intake	100
>48 h or when well	Usual daily amount	Gradual increase to usual full dietary intake	100

[a]Leucine-free and low fat for HMGCL (disorder **7.11**)

Comments/Additions

1. Families/individuals should start sick-day formula (to decrease leucine intake and suppress catabolism). Start carnitine if not used routinely. Fluids without calories or electrolytes should be avoided or intake minimized.
2. Monitor urine ketones, which will become positive with loss of metabolic control or inadequate caloric intake except in patients with HMGCL deficiency, who are unable to make ketones.
3. If the patient is unable to take in oral fluids and has persistent vomiting or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

- **7.6**: **Barth Syndrome**
  Symptomatic treatment includes cardiac medications as required, antibiotic drugs, and subcutaneous G-CSF if needed. Prevent hypoglycemia; monitor for lactic acidosis and (mild) hyperammonemia. The value of L-carnitine supplements or pantothenic acid has not been proven.
- **7.7**: **MEGDEL Syndrome**
  Individualize treatment. Prevent hypoglycemia, monitor for lactic acidosis. Avoid fasting and ensure adequate intake of energy (e.g., lipids). Patients may present with severe infections, not only in the neonatal period but also later in life.
- **7.8**: **Neonatal Mitochondrial Encephalocardiomyopathy**
  Individualize treatment. Patients may suffer from early onset of severe muscular hypotonia and cardiomyopathy along with hyperammonemia and lactic acidosis requiring intensive care. Fasting intolerance and low glucose tolerance (e.g., 3–4 mg/kg/min) must be anticipated. Fat tolerance is usually preserved and IV lipids (3.5 g/kg/day) are well tolerated. Data on the usage of conjugating agents such as sodium benzoate/phenylacetate in this condition is lacking.
- **7.9**: **Costeff Syndrome**
  Most patients do not become acutely ill.
- **7.10**: **Methylglutaconic Aciduria Type IV**
  Individualize treatment.

Comments/Additions

MGA types II–IV do not involve defects in the leucine pathway but affect mitochondrial functions through various pathomechanisms; treatment for patients with these forms of MGA is largely symptomatic.

- **7.11**: **3-Hydroxy-3-Methylglutaric Aciduria**
  - Emergency treatment (includes management of ill neonates)

  Management may be adapted from tables for disorders **7.4** (3-methylcrotonylglycinuria) and **7.5** (3-methylglutaconic aciduria type I) (see above). Prompt administration of carbohydrates/IV dextrose is mandatory. Intralipid is contraindicated.
- **Isoleucine Catabolic Pathway**
  - **7.12**: **2-Methylbutyrylglycinuria**[4]
  - **7.13**: **2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency**
  - **7.14**: **Beta-Ketothiolase Deficiency**
- **Valine Catabolic Pathway**
  - **7.15**: **Isobutyryl-CoA Dehydrogenase Deficiency**[4]
  - **7.16**: **3-Hydroxyisobutyryl-CoA Deacylase Deficiency**
  - **7.17**: **3-Hydroxyisobutyrate Dehydrogenase Deficiency**
  - **7.18**: **Methylmalonate Semialdehyde Dehydrogenase Deficiency**

Treatment is similar to the leucine pathway disorders except that isoleucine or valine reduced concentration formulae are required. Check carnitine status and add L-carnitine as required (e.g., 50–100 mg/kg/day). In patients with beta-ketothiolase deficiency (disorder **7.14**), oral or IV carbohydrate administration is most effective in suppressing ketogenesis; metabolic acidosis should be treated cautiously to prevent hypernatremia and paradoxical CNS acidosis.

[4]Patients not usually acutely ill.

Emergency treatment (includes management of ill neonates) for disorders 7.19, 7.20

Objective	Treatment
1. Treat dehydration	Normal saline bolus as clinically indicated. Start IV dextrose 10–12.5 % at 1–1.5 times maintenance; add NaCl and KCl depending on renal output and serum electrolyte levels. Plan rehydration over a 48 h period to prevent cerebral edema
2. Correct acidosis	Usually corrects with reestablishment of anabolic state. In extremis, give 1–2 mEq/kg of NaBicarbonate
3. Correct hyperglycemia (blood glucose >200 mg/dl)	Regular insulin drip, e.g., 0.05–0.1 units/kg/h until blood glucose is controlled
4. Reestablish anabolism	(a) If able to feed enterally, use Ile/Met/Thr/Val-free formula to provide total caloric intake of 120–150 % of maintenance (b) Adjust IV treatment as required (peripheral/central line) (c) 20 % fat emulsion, rate 1–3 g/kg/day IV (d) If NPO, use lowered Ile/Met/Thr/Val-free TPN
6. Metabolite conjugation and reduction	(a) L-carnitine 100 mg/kg/day IV or PO/NG[a] (b) Add metronidazole PO or NG for intermittent treatment (10 mg/kg/day for 1 week) (c) Urgently consider HD/HF in encephalopathic patients or if blood ammonia is ≥300–400 µmol/l, particularly if intensified treatment is insufficient over a period of 2–4 h[d]
7. Enhance residual enzyme activity	Cobalamin-responsive MMA: 1 mg hydroxycobalamin/dose IM daily[b, c]
8. Other	(a) Treat infections effectively. Note that neutropenia and thrombocytopenia are frequent findings during metabolic crisis (b) Monitor for further complications (e.g., cerebral edema, acute pancreatitis)

[a]Higher doses of L-carnitine have also been used (200–400 mg/kg/day). It is reasonable to increase the IV dose, e.g., when the patient undergoes HD/HF

[b]Each patient with MMA should be tested for B12 responsiveness by a trial of parenteral hydroxycobalamin in a dose of 1 mg/day. In those who respond, therapy is continued but the oral route may be used. Cyanocobalamin may be used if hydroxycobalamin is not available

[c]In PA, biotin responsiveness is doubtful. Biotin supplementation (10 mg daily) is therefore rarely beneficial

[d]N-carbamylglutamate may be started as a bridge, e.g., while waiting for HD/HF. In undiagnosed patients presenting with hyperammonemia, sodium benzoate/phenylacetate may be given but should be stopped once PA or MMA has been diagnosed (Chapman et al. 2012)

- **Disorder 7.19: Propionic Acidemia**
- **Disorder 7.20: Methylmalonic Acidemia**

Comments/Additions

1. Stop all natural protein sources initially, and then, reintroduce restricted natural protein by 24 h (0.2–0.5 g/kg/day) and begin addition of complete protein by 48 h with escalation to normal intake thereafter. Use additional Ile/Met/Thr/Val-free formula for adequate amino acid supply
2. Laboratory studies including blood gases, pH, ammonia, blood glucose, lactate, electrolytes, osmolality, plasma amino acids, acylcarnitines, ALT, AST, coagulation screen, CK, full blood count, urinary ketones and urinary organic acids, and any other laboratory tests indicated by the clinical history and examination

- **Disorder 7.21: Malonic Aciduria**
- **Disorder 7.22: Combined Malonic Aciduria and Methylmalonic Aciduria**

Protocol for intercurrent illness: initial measures for disorders 7.19, 7.20

Treatment	Ile/Met/Thr/Val-free special medical food	Natural food protein intake
First 24 h	1.2–1.5 times usual daily amount	None
24–48 h	1.2–1.5 times usual daily amount	None to half usual dietary intake
>48 h or when well	Usual daily amount	Gradual increase to usual full dietary intake

Emergency treatment (includes management of ill neonates) for disorders 7.21, 7.22

Objective	Treatment
1. Treat hypoglycemia	Give IV glucose bolus (e.g., 2 ml/kg of dextrose 10 %); start IV dextrose 10–12.5 % at maintenance and add NaCl and KCl depending on serum electrolyte levels
2. Metabolite conjugation	Carnitine: 100 mg/kg/day in three divided doses IV or PO
3. Correct acidosis	Usually corrects with reestablishment of anabolic state. In extremis, give 1–2 mEq/kg of NaBicarbonate
4. Other	(a) Monitor cardiac function (b) Monitor for further complications (e.g., lactic acidemia, seizures)

There is limited experience in managing this condition

Comments/Additions

1. If the patient is feeding orally, increase the amount of calories from carbohydrate relative to fat, introduce MCT fat, and prevent fasting.
2. Laboratory studies including blood gases, pH, blood glucose, lactate, electrolytes, full blood count, osmolality, CK, ALT, AST, acylcarnitines, cholesterol, ketones and urinary organic acids, and any other laboratory tests indicated by the clinical history and examination.

Chronic Treatment

- **Disorder 7.1: Branched-Chain Amino Acid Transferase Deficiency**
  - The existence of this disorder in humans remains in question.
- **Disorder 7.2: Maple Syrup Urine Disease**

Standard treatment for disorder 7.2

No.	Disease/Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.2	MSUD – severe forms (MSUD 1A, 1B, 2)	All ages	Lowered BCAA diet[a] Isoleucine and valine supplements[b] Glutamine and alanine[c]	See table below Adjusted to blood levels 100–250 mg/kg/day each	Leucine 100–300 μM Isoleucine 150–350 μM Valine 200–400 μM[h] Glutamine 400–800 μM Alanine 150–500 μM
			NaCl[d] Thiamine[e]	3–5 mEq/kg/day 50–300 mg/day	Within normal limits
7.2	MSUD – milder forms (1A, 2)	All ages	Reduced natural protein diet[f] Multivitamin with minerals Thiamine[e]	See table below As required 50–300 mg/day	See above (severe forms)
7.2	MSUD – thiamine-responsive forms (MSUD 2)	All ages	Reduced natural protein diet[f] Multivitamin with minerals Thiamine	See table below As required 10 mg/kg/day (50–500 mg/day)	See above (severe forms)
7.2	MSUD 3 (combined dehydrogenases deficiency)	All ages	See above (severe forms)[g]		See above (severe forms)

[a]Special medical food devoid of the branched-chain amino acids and enriched with micronutrients (see table nutritional treatment for patients with maple syrup urine disease below)
[b]Typically as 10 mg/ml solutions
[c]Supplements of glutamine and alanine may also be given (100–250 mg/kg/day each). Calculate the amount present in the diet, and add supplements to meet the recommended intake
[d]Calculate the amount present in the diet, and add supplements to meet the recommended intake
[e]Thiamine given until molecular genotype is known. Not given in patients with the Mennonite mutation Y393N (Morton et al. 2002)
[f]Protein intake of approximately 1.5–2.0 g/kg/day in young infants and 0.6–1.5 g/kg/day in older children and adults
[g]Attempts at treatment with diet and cofactors have been unsuccessful in some patients in preventing CNS deterioration; usually not thiamine responsive
[h]Target ratios of approximately 1:2:2 for leucine, isoleucine, and valine, respectively

Comments/Additions

1. Intake of whole protein and supplements of individual amino acids are adjusted based on plasma quantitative amino acids levels and individual needs 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.

- **Disorder 7.3: Isovaleric Acidemia**

Standard nutritional treatment for patients with maple syrup urine disease

Age	Total protein requirement[a] (g/kg/day)	Leucine tolerance[b] (mg/kg/day)	Isoleucine intake (mg/kg/day)	Valine intake (mg/kg/day)	Energy requirement[c] (kcal/kg/day)
Neonates	2.7–3.5	40–100	30–90	40–95	100–145
Infants	2.5–3.2	35–75	20–70	30–80	80–135
Young children	1.8–2.6	20–65	10–30	20–50	60–130
Older children and adults	1.4–1.8	5–50	5–30	15–30	35–70

Modified from Strauss et al. (2010); Acosta and Yannicelli (2001) and Marriage (2010). These recommendations are only a guide and must be individualized for each patient, based on the severity of their disorder, actual needs, and blood quantitative amino acid levels
[a]Includes protein intake from special medical foods devoid of BCAA plus that from natural whole protein sources
[b]Leucine (mg/kcal ratio of 0.5–0.8 for neonates, 0.4–0.6 for infants; ratio of 0.25–0.30 in children and older)
[c]Lipids should comprise 40–50 % of total calories. Formula concentrations over 24 kcal/oz may result in loose stools, diarrhea, and dehydration

Standard treatment for disorder 7.3

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.3	IVA – severe forms	All ages	Lowered leucine diet[a]	See tables below	Leucine 50–180 μM or normal range for laboratory
			L-carnitine	100 mg/kg/day in three doses[c]	Normal to high normal range for free carnitine
			Glycine	250 (150–300) mg/kg/day in three doses[d]	Glycine 200–400 μM
7.3	IVA – mild forms	All ages	Reduced natural protein diet[b]	See tables below	
			Multivitamin with minerals	As required	
			L-carnitine	30–100 mg/kg/day in three doses[c]	Normal free carnitine
			Glycine	150–250 mg/kg/day in three doses[d, e]	Glycine 200–400 μM

[a]Special medical food devoid of leucine and enriched with micronutrients 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 sufficient to maintain metabolic control should be used

[b]Natural protein intake of approximately 1.5–2.0 g/kg/day in young infants and 0.6–1.5 g/kg/day in older children and adults. Patients with a mild IVA form and the missense mutation 932C > T (A282V) usually do not require protein restriction

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

[d]Glycine is often omitted from chronic therapy. If used, it is added to the daily special formula as weighed dry powder or 100 mg/ml solution

[e]Patients with a mild IVA form may not require glycine supplements

Standard nutritional treatment for patients with isovaleric acidemia

Age	Protein requirement[a] (g/kg/day)	Leucine intake[b] from whole natural protein (mg/kg/day)	Energy requirement[c] (kcal/kg/day)
Neonates	2.5–3.5	65–150	95–145
Infants	2.0–3.0	50–140	80–135
Young children	1.5–2.0	40–90	60–130
Older children and adults	1.1–1.8	30–60	35–70

Modified from Acosta and Yannicelli (2001) and Marriage (2010). These recommendations are only a guide and must 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

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

[b]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

[c]Formula concentrations over 24 Kcal/oz may result in loose stools, diarrhea, and dehydration

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, losses, 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 allowing metabolic control should be used in order to avoid over-treatment and leucine deficiency.

- **Disorder 7.4: Methylcrotonylglycinuria**

Standard treatment for disorder 7.4

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.4	3MCCC1 3MCCC2	All ages	Lowered leucine diet[a]	See tables for IVA (disorder **7.3**)	Leucine 50–180 μM or normal range for laboratory
			L-carnitine	50–100 mg/kg/day in two to three doses[b]	Normal free carnitine

[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 usually not given, though it might be considered in severe cases (175–250 mg/kg/day) as it increases 3-methylcrotonylglycine excretion

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

Comments/Additions

1. Special medical food devoid of leucine and enriched with micronutrients 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 allowing metabolic control should be used.
2. Patients are not responsive to biotin therapy.
3. Asymptomatic individuals may not need dietary restrictions or L-carnitine but may occasionally need blood and urine monitoring.

- **Disorder 7.5: 3-Methylglutaconic Aciduria, Type I**

Standard treatment for disorder 7.5

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.5	3MG1	All ages	L-carnitine	100 mg/kg/day in three doses[a]	Normal free carnitine
			Lowered leucine diet[b]	See tables for IVA (disorder **7.3**)	Leucine 50–180 µM or normal range for laboratory

[a]Calculate the amount present in the special medical food if used, and add supplements to this to meet the recommended intake
[b]No dietary regimen has been therapeutically proven. Special medical food devoid of leucine may be used for severe forms of the disorder. Patients with milder forms of the disorder might require a reduced natural protein intake. The least restrictive diet allowing metabolic control should be used

Comments/Additions

1. See comment 1 for disorder **7.3**.

- **Disorder 7.6: Barth Syndrome**
  Symptomatic treatment includes cardiac medications as required, prophylactic antibiotic drugs, and subcutaneous G-CSF if needed (e.g., in patients with symptomatic neutropenia). Cornstarch supplements at bedtime may be used to prevent hypoglycemia. The value of L-carnitine supplements or pantothenic acid has not been proven.
- **Disorder 7.7: MEGDEL Syndrome**
  Individualize treatment. Avoid fasting and ensure adequate intake of energy. Patients may present with severe infections, not only in the neonatal period but also later in life.
- **Disorder 7.8: Neonatal Mitochondrial Encephalocardiomyopathy**
  Individualize treatment. Avoid fasting and ensure adequate intake of energy. Monitor for lactic acidosis and hyperammonemia. Frequent feeding and administration of fats as a main source of energy might prevent or attenuate a metabolic crisis.
- **Disorder 7.9: Costeff Syndrome**
  Symptomatic treatment.
- **Disorder 7.10: Methylglutaconic aciduria type IV**
  Individualize treatment.
- **Disorder 7.11: 3-Hydroxy-3-Methylglutaric Aciduria**

Standard treatment for disorder 7.11

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.11	HMGCL	All ages	Lowered leucine and fat, high-carbohydrate diet[a]	See tables for IVA (disorder **7.3**) Of note, fat is limited to 20–25 % of total daily caloric intake	Leucine 50–180 µM or normal range for laboratory
			L-carnitine	100 mg/kg/day in three doses	Normal free carnitine

[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. Avoid fasting. The least restrictive diet that allows metabolic control should be used

Comments/Additions

1. See comment 1 for disorder **7.3**.
2. In addition to leucine restriction, daily caloric intake of fat is limited to 20–25 % of total caloric intake per day. Use a leucine-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 added to the special metabolic formula may be used to prevent hypoglycemia.

- **Disorder 7.12: 2-Methylbutyrylglycinuria**
- **Disorder 7.13: 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency**
- **Disorder 7.14: Alpha-Methylacetoacetic Aciduria**
- **Disorder 7.15: Isobutyryl-CoA Dehydrogenase Deficiency**
- **Disorder 7.16: 3-Hydroxyisobutyryl-CoA Deacylase Deficiency**
- **Disorder 7.17: 3-Hydroxyisobutyrate Dehydrogenase Deficiency**
- **Disorder 7.18: Methylmalonate Semialdehyde Dehydrogenase Deficiency**

Standard nutritional treatment for patients with disorders limited to isoleucine or valine

Age	Isoleucine intake[a]	Valine intake[b]	Natural protein requirement[c] (g/kg/day)	Total protein requirement (g/kg/day)	Energy requirement (kcal/kg/day)
Neonates	90–150 mg/kg/day	65–110 mg/kg/day	1.5–2.5	2.8–3.5	95–145
Infants	50–115 mg/kg/day	40–90 mg/kg/day	1.2–2.0	2.5–3.2	80–135
Young children	630–1,250 mg/day	600–1,100 mg/day	0.8–1.5	1.8–2.6	60–130
Older children and adults	965–1,900 mg/day	900–2,015 mg/day	0.5–1.4	1.4–1.8	35–70

Modified from Yanicelli (2010). These recommendations are only a guide and must be individualized for each patient, based on the severity of their disorder, actual needs, and blood quantitative amino acid levels

[a]The targets relating to isoleucine curtailment would apply to MBD deficiency (disorder **7.12**), MHBD deficiency (disorder **7.13**), and in principle to beta-ketothiolase deficiency (disorder **7.14**)

[b]The targets relating to valine curtailment would apply to MMSDH deficiency (disorder **7.18**), HIBDH deficiency (disorder **7.17**), IBD deficiency (disorder **7.15**), and in principle to HIBCH deficiency (disorder **7.16**)

[c]In addition to the natural protein intake, special medical food (devoid of Ile or Val as appropriate) provides adequate total protein intake. The least restrictive diet should be used. These are approximate therapeutic strategies, and individual patients' requirements may vary substantially. Also, for a given patient, variations must be anticipated in relationship to growth rate, physical activity, intercurrent illness etc

Monitor carnitine status and add L-carnitine as required (e.g., 50–100 mg/kg/day)

In beta-ketothiolase deficiency (disorder **7.14**): avoid fasting and high-fat intake; carbohydrate-rich meals and frequent feeding have been effective to avoid ketonuria

- **Disorder 7.19: Propionic Acidemia**
- **Disorder 7.20: Methylmalonic Acidemia**

Standard treatment for disorder 7.19 and 7.20

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
7.19	PA	All ages	Lowered Ile/Val/Met/Thr diet[a]	See table below	Low normal to normal range of age for laboratory for Ile/Val/Met/Thr[b]; normal ammonia; normal acid–base status
			L-carnitine	100 mg/kg/day in three doses	Normal to high normal range for free carnitine
			Metronidazole	10 mg/kg/day for intermittent treatment PO[c, d]	
7.20	MMA	All ages	Lowered Ile/Val/Met/Thr diet[a]	See table below	Low normal to normal range of age for laboratory for Ile/Val/Met/Thr[b]; normal plasma ammonia; normal acid–base status
			L-carnitine	100 mg/kg/day in three doses	Normal to high normal range for free carnitine
			In cobalamin-responsive MMA: hydroxycobalamin	1 mg/day IM[e]	
			Metronidazole	10 mg/kg/day for intermittent treatment PO[c]	
			In renal failure: symptomatic therapy	As required	

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

[a]Individualize depending upon tolerance to protein, growth, and nutritional adequacy, guided by parameters in table standard nutritional treatment for propionic acidemia and methylmalonic acidemia below

[b]Provide an adequate intake; prevent deficiencies

[c]Short course or intermittent treatment (e.g., 1 week per month; >6 months)

[d]In PA, biotin responsiveness is doubtful and supplementation rarely beneficial

[e]Each patient with MMA should be tested for B12 responsiveness by a trial of parenteral hydroxycobalamin in a dose of 1 mg/day IM. In those that respond (decrease in urinary MMA excretion by ≥50 %), therapy is continued but the oral route may be used and the dose may be adjusted. Cyanocobalamin may be used if hydroxycobalamin is not available

Standard nutritional treatment for propionic acidemia and methylmalonic acidemia

Age	Isoleucine intake	Methionine intake	Threonine intake	Valine intake	Natural protein requirement[a] (g/kg/day)	Total protein requirement[b] (g/kg/day)	Energy requirement[c]
Neonates	60–110 mg/kg/day	20–50 mg/kg/day	50–125 mg/kg/day	60–105 mg/kg/day	1.2–1.8	2.7–3.5	125–145 kcal/kg/day
Infants	40–90 mg/kg/day	15–40 mg/kg/day	20–75 mg/kg/day	40–80 mg/kg/day	0.8–1.5	2.5–3.2	115–140 kcal/kg/day
Young children	485–735 mg/day	275–390 mg/day	415–600 mg/day	550–830 mg/day	0.7–1.2	1.8–2.6	900–1,800 kcal/day
Older children and adults	630–1,470 mg/day	360–950 mg/day	540–1,455 mg/day	720–2,000 mg/day	0.5–0.8	1.4–1.7	1,500–3,200 kcal/day

Modified from Yanicelli 2010. These recommendations are only a guide and must be individualized for each patient, based on the severity of their disorder, actual needs, and blood quantitative amino acid levels

[a]In addition to the whole protein, specialized formulas (devoid of Ile/Met/Thr/Val) are needed. Of note, individual patients' requirements may vary substantially

[b]Includes protein intake from special medical foods devoid of Ile/Met/Thr/Val plus that from natural whole protein sources. Total protein recommendation is higher when the majority of protein is supplied by free amino acids (Ile/Met/Thr/Val-free formula). However, patients with hyperammonemia or MMA patients with renal impairment require carefully adjusted protein amounts

[c]Energy requirement is usually lower during well state compared with unwell state in patients

- **Disorder 7.21 Malonic Aciduria**
- **Disorder 7.22 Combined Malonic Aciduria and Methylmalonic Aciduria**

Standard treatment for disorder 7.21 and 7.22

No.	Symbol	Age	Medication/diet	Dosage[a, b]	Target plasma levels
7.21	MA	All ages	High-carbohydrate and low long-chain triglycerides (LCT) fat diet; medium-chain triglycerides (MCT) fat supplements	Dietary fat may comprise 30–50 % LCT and 50–70 % MCT	Normal blood glucose, normal essential fatty acids, normal cholesterol
			L-carnitine	100 mg/kg/day in three doses	Normal free carnitine
7.22	CMAMMA	All ages	High-carbohydrate and low long-chain triglycerides (LCT) fat diet; medium-chain triglycerides (MCT) fat supplements; moderate restriction of natural protein	Dietary fat may comprise 30–50 % LCT and 50–70 % MCT	Normal blood glucose, normal essential fatty acids, normal cholesterol
			L-carnitine	100 mg/kg/day in two to three doses	Normal free carnitine

Little information published and effectiveness of treatment has yet to be determined

[a]There are no established treatment recommendations and dosage may vary considerably

[b]Check whether metabolite levels are responsive to (moderate) protein restriction in patients with combined malonic aciduria and methylmalonic aciduria (disorder **7.22**)

Comments/Additions

1. Avoid fasting to prevent hypoglycemia.
2. The management of a patient with cardiomyopathy should be done in consultation with a cardiologist; a beta-blocker or angiotensin converting enzyme inhibitor or other medications might be given depending on individual needs.
3. Cholesterol supplementation should be given in patients with reduced cholesterol levels.

Experimental Treatment[5]

Disorder no.	Symbol	Substance
7.2	MSUD	Coenzyme Q10 (5 mg/kg/day; electron carrier of the respiratory chain with antioxidant properties; in addition to standard therapy during crisis)[a]
	MSUD 1A	Phenylbutyrate (500 mg/kg/day; to activate E1α/BCKDC enzyme activity; in addition to standard therapy)[b]
7.19	PA	Citric acid (as K-Na-hydrogen citrate, 80–120 mg/kg/day PO; might improve TCA cycle flux; in addition to standard therapy during crisis with lactic acidosis)[c]

[a]Knerr et al. (2011)

[b]Brunetti-Pierri et al. (2011)

[c]Siekmeyer et al. (2013)

[5]This excludes organ transplantation (see Mazariegos et al. 2012 and special literature).

Standard Therapy and Emergency Therapy Flow Charts
Disorders **7.1–7.22**

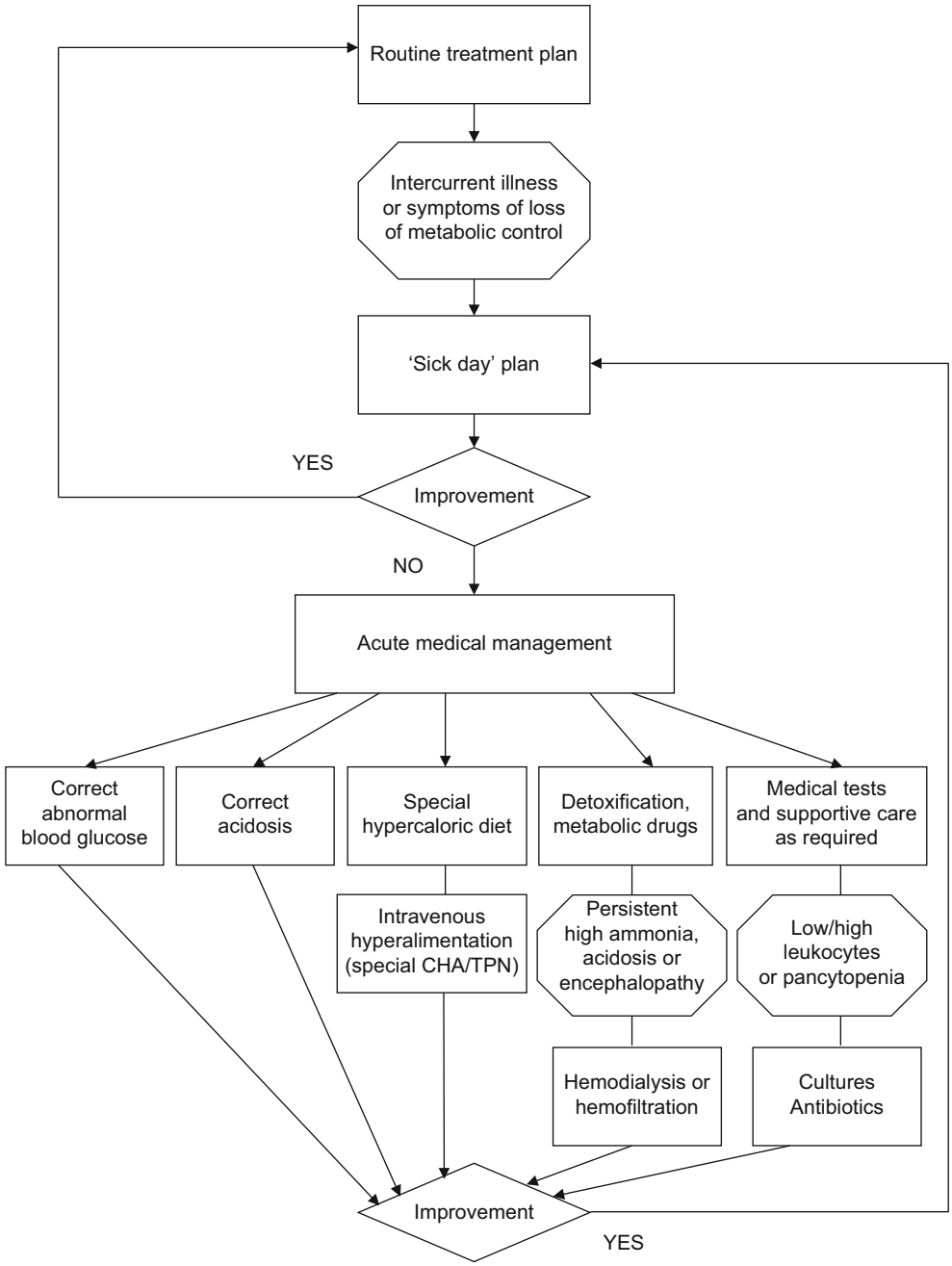

Fig. 7.3 Management of patients with disorders of BCAA metabolism[a]

[a]These are approximate guidelines, and individual patients' requirements may vary substantially

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