Organic Acidemias

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Core Messages

- Organic acidemias (OA) are defects in the degradation of leucine, isoleucine, and valine.
- OA can present as either a severe neonatal onset form (poor feeding, vomiting, lethargy, tachypnea, progressing to acidosis, respiratory distress, coma, death) or late-onset (usually recurrent ketoacidosis or lethargy with catabolic stress).
- Nutrition treatment involves use of propiogenic amino acid free medical foods and restriction of natural protein in PROP and MMA and protein restriction with or without leucine-free medical food and supplemental glycine in IVA.
- Outcomes in PROP and MMA have been guarded with frequent neurological complications, renal dysfunction, cardiomyopathy and optic atrophy but are improving with earlier identification and treatment, as well as with liver or liver-kidney transplantation; outcomes in IVA are often normal.

18.1   Background

Organic acidemias are disorders of branched chain amino metabolism in which non-amino organic acids accumulate in serum and urine. They are defects in the degradation pathways of leucine, isoleucine, and valine. These conditions are usually diagnosed by examining organic acids in urine with abnormal metabolites also notable on acylcarnitine profile. Organic acidemias comprise a variety of disorders and include methylmalonic acidemia (MMA), propionic acidemia (PROP), isovaleric acidemia (IVA), glutaric acidemia, type 1 (GA-1), 3- methylcrotonyl carboxylase deficiency (3-MCC), 3-methylglutaconic acidemia (3-MGA), methylmalonyl-CoA epimerase deficiency (MCEE), and vitamin B_{12} uptake, transport, and synthesis defects [1–3].

All are autosomal recessive with the exception of the rare, x-linked disorder, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBD). The two primary disorders of isoleucine and valine catabolism are propionic acidemia (PROP) and methylmalonic acidemia (MMA) and the primary organic acidemia of leucine catabolism is isovaleric acidemia (IVA). These three disorders will be discussed in detail in this chapter. GA-1 is addressed in Chaps. 19 and 20. The incidence of MMA ranges from 1:83,000 in Quebec to 1:115,000 in Italy to 1:169,000 in Germany and that of PROP from 1:17,400 in Japan to 1:165,000 in Italy to 1:277,000 in Germany [4–7]. On the basis of newborn screening data, the incidence of IVA has a range of 1:62,500 live births in Germany to ~1:250,000 in the United States [7, 8]. Newborn screening via tandem mass spectrometry has allowed earlier diagnosis and has revealed a higher incidence of these disorders than previously noted based on clinical presentation suggesting a broader phenotype with milder and/or asymptomatic individuals [4, 5, 7, 9–13]. Techniques for newborn screening continue to be refined to aid in increased sensitivity and specificity of screening [14, 15].

The oxidation of threonine, valine, methionine, and isoleucine results in propionyl-CoA, which propionyl-CoA carboxylase converts into L-methylmalonyl-CoA, which is metabolized through methylmalonyl-CoA mutase to succinyl-CoA. Whereas the breakdown of the above amino acids is felt to contribute to ~50% of the propionyl-CoA production, gut bacteria and the breakdown of odd-chain-length fatty acids also substantially contribute to propionyl-CoA production (~ 25% each) with a minimal contribution by cholesterol metabolism [16–19] (Fig. 18.1).

PROP is caused by a deficiency of the mitochondrial enzyme, propionyl-CoA carboxylase (PCC) [9, 19]. The enzyme is composed of two subunits, an alpha and beta subunit, each encoded by a different gene, *PCCA* and *PCCB*, respectively [9]. The enzyme is biotin-dependent with biotin binding to the alpha subunit [19, 20]. Deficiency of the enzyme results in the accumulation of propionyl-CoA and increased concentrations of free propionate in blood and urine. Identification of methylcitrate and 3-hydroxypropionate are the major diagnostic metabolites seen on organic acid analysis [19,
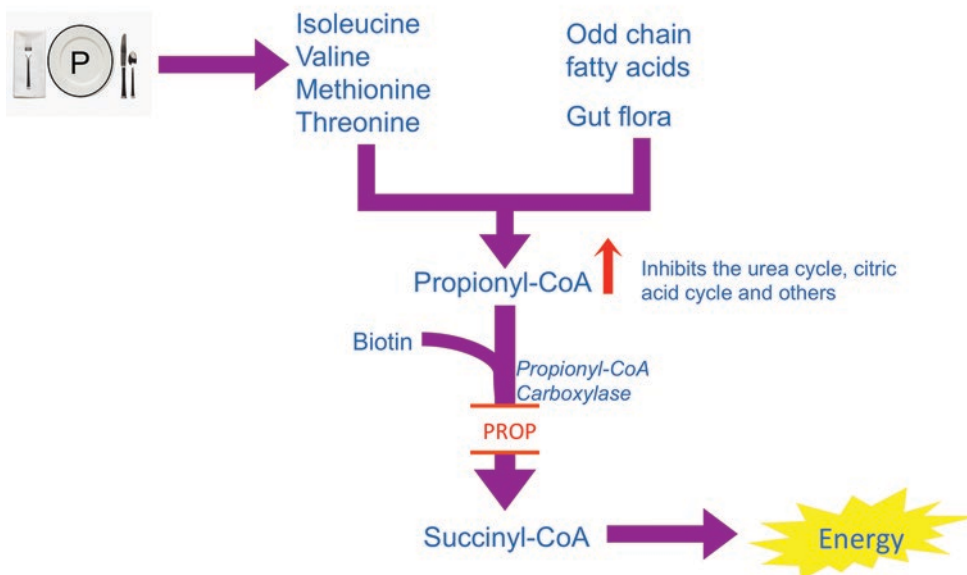
Fig. 18.1 Metabolic pathway of propionic acidemia (PROP)

21]. Elevation of propionylcarnitine (C3) can be seen on acylcarnitine profile [9, 21].

Classic MMA is caused by a deficiency of the enzyme, methylmalonyl-CoA mutase, an adenosylcobalamin (AdoCbl)-dependent enzyme consisting of two identical subunits (2α) [9, 19, 21] (Fig. 18.2). About 50% of cases of MMA are due to a defect in the mutase apo-enzyme; in others, it is due to a defect in the uptake, transport, or synthesis of its adenosyl-B_{12} coenzyme causing variant forms of MMA that may or may not be associated with homocystinuria. Individuals who are deficient in mutase activity may be further designated as mut⁻ or mut⁰ pending residual enzyme activity [19]. There is good correlation between residual enzyme activity and severity of the clinical phenotype [21]. Acquired methylmalonic aciduria can also be seen with acquired deficiency of vitamin B_{12} in pernicious anemia and in transcobalamin II deficiency [9]. Hence, vitamin B_{12} deficiency must be excluded in all individuals

with elevated methylmalonic acid concentrations [9, 19]. Deficiency of the mutase enzyme results in the accumulation of methylmalonyl-CoA and propionyl-CoA and is reflected in elevations of methylmalonic acid and propionic acid in blood and urine [19, 21]. Methylmalonic acid, methylcitrate, 3-hydroxypropionate, and 3-hydroxyisovalerate are found on urine organic acid analysis [9, 19, 21]. Propionylcarnitine (C3) is also found on acylcarnitine profile in MMA [9, 21].

IVA was initially described in 1966 and was the first organic acidemia described. IVA is caused by a deficiency of the enzyme, isovaleryl-CoA dehydrogenase, an enzyme important in leucine catabolism and also important in the transfer of electrons to the respiratory chain [9, 19]. The consequent accumulating metabolites include isovaleric acid, isovalerylglycine, 3-hydroxyisovaleric acid, and isovalerylcarnitine (C5) [9, 19] (Fig. 18.3). These are easily identified on urine organic acid analysis and the

Methylmalonic Acidemia (MMA)

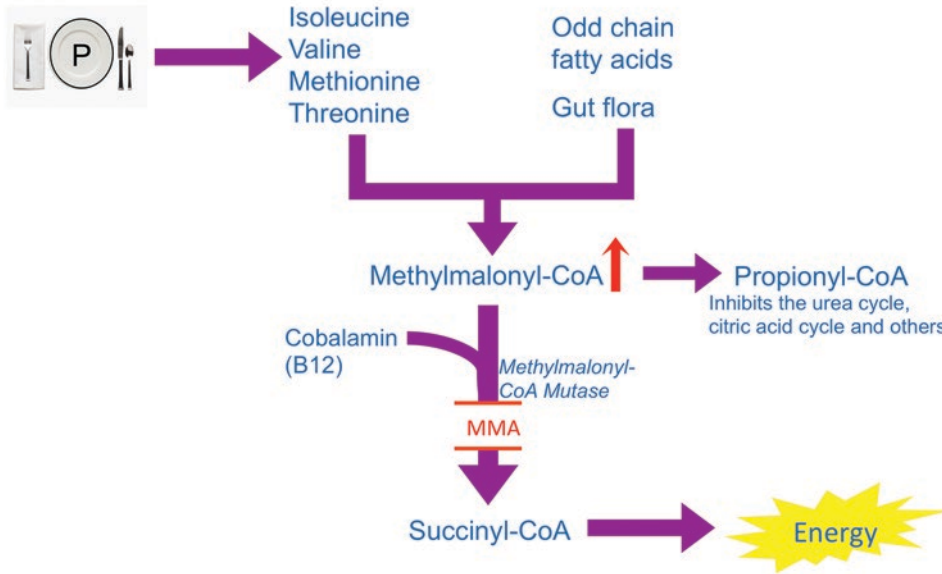*Occurring across tissues including liver…*

Fig. 18.2 Metabolic pathway of methylmalonic scidemia (MMA)

Isovaleric Acidemia (IVA)

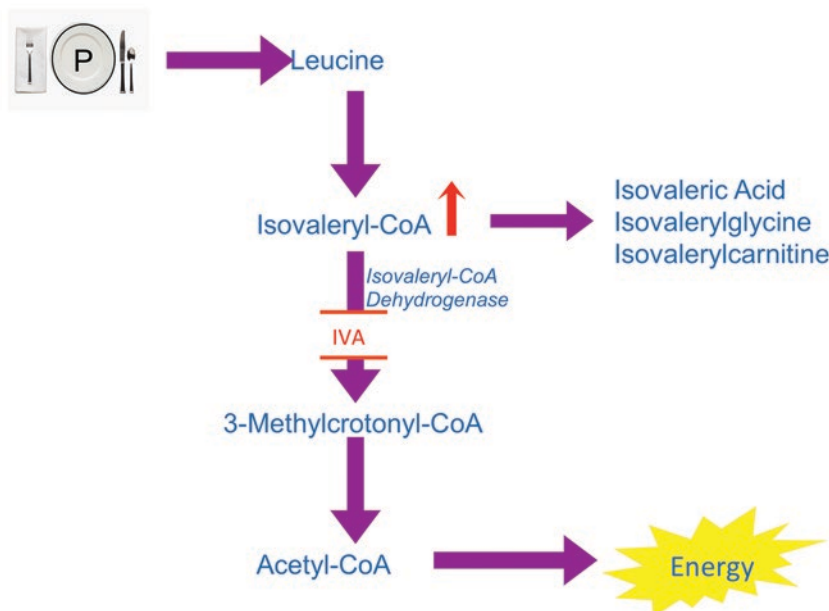*Occurring across tissues including liver and kidney…*

Fig. 18.3 Metabolic pathway of isovaleric acidemia (IVA)

latter on acylcarnitine profile. The excretion of isovalerylglycine and 3-hydroxyisovaleric acid are diagnostic.

18.2 Clinical Presentation

Organic acidemias may present at any age. In general, they can be divided into two broad groups—a severe, neonatal presentation and a chronic late-onset presentation.

18.2.1 Severe Neonatal Onset Form

The clinical presentation of the severe, neonatal onset form of these disorders can be quite similar for all three disorders. As is typical with inborn errors of metabolism, the pregnancy and birth history for the child is often unremarkable. Following an initial symptom-free period which may last from hours to weeks, the infant then develops nonspecific symptoms, such as poor feeding, vomiting, dehydration, lethargy, tachypnea, and hypothermia and if unrecognized, quickly progresses to respiratory distress, apnea, bradycardia, coma, cerebral edema, and death [9, 13, 16, 19, 21]. Despite newborn screening, many children are critically ill at the time of initial presentation [13]. At the time of presentation, the physical examination is primarily one of altered mental status and encephalopathy, but dehydration, hepatomegaly, abnormal tone, and seizure-like activity may also be seen [9, 13, 16, 19]. A sweaty feet or dirty sock smell is classically described for IVA secondary to excretion of 3-hydroxyisovaleric acid [9–11]. An antenatal presentation of PROP with nephromegaly and acute neonatal kidney injury has also been reported [22].

18.2.2 Chronic Late Onset Form

The late onset form typically presents after 30 days of age and maybe much later including into adolescence or adulthood [19]. McCrory et al. noted one-third of patients with PROP were ascertained by clinical presentation after one year of age [13].

Individuals may present with recurrent attacks of ketoacidosis with coma or lethargy and ataxia during times of catabolic stress such as during an illness or following a high protein meal [9, 19]. The presentation may mimic diabetic ketoacidosis [23–26]. Childhood and adolescent onset patients have presented with chronic renal failure [27]. Other individuals may present with acute hemiplegia, hemianopsia, or cerebral edema, or symptoms that mimic a cerebral vascular accident, cerebral tumor, or acute encephalitis [13, 19]. In addition, symptoms may simulate a neurologic disorder presenting with hypotonia, weakness, ataxia, seizures, progressive spasticity, movement disorder, vision loss, or developmental delay. Symptoms may also be misdiagnosed as a gastrointestinal disorder secondary to presenting with failure to thrive, anorexia, chronic vomiting, or a Reye-like presentation [9, 13, 19, 21, 27]. Some individuals may present with hematologic manifestations or present with recurrent infections [9, 19]. Adult presentations have included acute metabolic acidosis with renal and respiratory failure [28] and isolated dilated cardiomyopathy [29].

18.2.3 Laboratory Studies and Diagnosis

Laboratory studies typically reveal a severe metabolic acidosis with an elevated anion gap, ketosis, and hyperammonemia [9, 16, 19, 21]. Hyperuricemia, hyperlacticacidemia, and hypocalcemia may also be seen. Blood glucose can be reduced, normal, or elevated [16, 19]. Bone marrow involvement as reflected by neutropenia, anemia, thrombocytopenia, or pancytopenia can also be observed and is a rather unique finding of organic acidemias [9, 16, 19]. Diagnostic metabolites, as noted above, are seen on urine organic acid analysis and acylcarnitine profile. Quantitative plasma amino acids and urine amino acids are useful to investigate the possibility of combined MMA and homocystinuria due to vitamin B_{12} synthesis defects. Striking elevations of glycine and alanine can be seen in blood and urine and may be an early clue to diagnosis and explains the historical descriptive term of "ketotic hyperglycinemias" [9, 21]. The

diagnosis may be confirmed by enzyme assay or molecular studies. Organic acidemias are increasingly identified via newborn screening with elevations in propionylcarnitine (C3) for PROP and MMA and elevated isovalerylcarnitine (C5) for IVA.

18.2.4 Complications

Organic acidemias are multisystem disorders with individuals at risk for a variety of complications. Complications arise despite apparent good metabolic control [30–32]. Neurologic complications include metabolic stroke with edema evolving into necrosis of the basal ganglia, especially the globus pallidus, and leading to a disabling movement disorder, motor dysfunction, and hypotonia [19, 21, 33–35]. Cortical volume loss, basal ganglia lesions, cerebral and vermian atrophy, and delayed myelination may be seen on neuroimaging [9, 19, 21, 34, 36, 37]. Restricted diffusion may be noted during acute events [36]. Clinically, seizures, deafness, optic nerve atrophy, neuropathy, myopathy, developmental delay, attention deficit-hyperactivity disorder (ADHD), and autistic features are seen [33, 35, 38–41] (Box 18.1). One study reported approximately 50% of affected individuals have an IQ < 80 [33], while another study suggested >70% of individuals with PROP have cognitive deficits [42]. The etiology of this neurologic damage is unclear. Theories include direct toxic effects of methylmalonic acid, propionic acid, and methylcitrate, impairment of energy metabolism as mediated by synergistic inhibition of the Krebs cycle and mitochondrial respiratory chain by the three metabolites, accumulation of decarboxylates in the central nervous system, neuroinflammation, interference of cytoskeleton assembly in neuronal and glial cells, and disruption of signaling pathways that promote apoptosis of neuronal cells [30, 42–50]. Elevations in lactate and ammonia in plasma and lactate, glutamine, glycine, and alanine in cerebrospinal fluid have also been detected in a patient with neurologic symptoms but no signs of catabolism suggesting that neurologic abnormalities may be related to localized metabolic derangements [31, 51]. Data suggests a synergistic effect of methylmalonic acid and ammonia disturbing the redox homeostasis and causing morphological brain abnormalities, including vacuolization, ischemic neurons, and pericellular edema in a rat model [52]. Propionate accumulation also results in morphological alterations in cerebral cortex astrocytes [35].

Another complication of organic acidemias is renal tubular acidosis with hyperuricemia leading to chronic renal impairment and eventually to renal failure [9, 19, 40] (Box 18.2). This is espe-

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Box 18.1: Neurological Complications of Organic Acidemias
- Metabolic stroke with edema evolving into necrosis of the basal ganglia and globus pallidus which leads to disabling movement disorder, motor dysfunction and hypotonia
- Cerebral atrophy and delayed myelination
- Seizures
- Optic nerve atrophy, deafness
- Neuropathy or skeletal myopathy
- Developmental delay, autistic features

Box 18.2: Complications of Organic Acidemias
- Renal tubular acidosis (RTA) with hyperuricemia; chronic renal impairment leading to renal failure
- Superficial desquamation and alopecia due to nutrient or essential amino acid deficiency
- Cardiomyopathy, long QT syndrome
- Pancreatitis – acute, chronic and/or recurrent
- Carnitine deficiency
- Osteopenia or osteoporosis
- Ovarian failure
- Liver disease including nonalcoholic steatohepatitis, fibrosis, and cirrhosis
- Possible increased risk of infections

cially prominent in individuals with MMA; however, renal disease and failure have also been reported in individuals with propionic acidemia with an age-dependent decline [53–56]. Renal histology reveals tubulointerstitial nephritis with fibrosis, tubular atrophy, and mononuclear inflammatory infiltrate [55, 57–59]. Renal disease is found in the majority of individuals with MMA who are over 6 years of age and may be due to chronic glomerular hyperfiltration secondary to excessive methylmalonic acid excretion [10, 19, 34, 46]. The risk of developing renal failure seems to correlate with methylmalonic acid exposure over time and depends on the disease type with mutase-deficient patients at greater risk than patients with cobalamin defects [58]. Thus, minimizing renal injury may require strict metabolic control to maintain methylmalonic acid concentrations as low as possible [19].

Furthermore, cardiomyopathy, more common in PROP than MMA and more commonly dilated than hypertrophic, may occur during acute decompensations or be the presenting feature and may be rapidly fatal [19, 60–64]. The pathogenesis of the cardiomyopathy is unclear—carnitine or micronutrient deficiency, infection, or acute energy deprivation have all been postulated [21, 32, 51]. Cardiomyopathy appears to develop independent of any specific metabolic profile and appears to occur at any age [32, 51, 62]. The mean age of presentation in one series was 7 years [62]. Long QT syndrome (delayed repolarization of the heart) is also reported and may occur in as high as 70% of patients with PROP [32, 65–68].

A secondary carnitine deficiency due to accumulation of propionyl-CoA and increased concentration of acylcarnitines is also common [19]. Superficial desquamation, alopecia, and corneal ulcerations similar to staphylococcal scalded skin syndrome or acrodermatitis enteropathica-like syndrome, typically associated with diarrhea, may be seen secondary to acute protein malnutrition or essential amino acid deficiency, especially isoleucine deficiency [51, 69–71]. Immune dysfunction has also been suggested with an increased risk for viral or bacterial infections, but good studies are lacking [51]. Chronic moniliasis has

been described and reflects the effect of propionyl-CoA and methylmalonate on T-cell number and function [9]. Finally, acute, chronic, and recurrent pancreatitis, osteopenia or osteoporosis, ovarian failure, and liver abnormalities including nonalcoholic steatohepatitis, fibrosis, and cirrhosis may also occur; the etiologies of which remain unclear [9, 21, 32, 40, 51, 54, 72–79].

18.3 Pathophysiology

The pathogenesis of the clinical features of organic acidemias remains complex and incompletely understood. The metabolic blocks cause metabolite accumulation triggering an endogenous intoxication. Propionyl-CoA and its metabolites inhibit the Krebs cycle resulting in reduced GTP and ATP synthesis, inhibit potassium channel flow, and are known to have inhibitory effects on pyruvate dehydrogenase complex, succinyl-CoA synthetase, ATP-citrate lyase, and N-acetyl-glutamate synthetase activities, and on the glycine cleavage system [9, 17, 18, 42, 80, 81]. Furthermore, methylmalonyl-CoA is known to inhibit pyruvate carboxylase [17, 82, 83]. Similarly, isovaleric acid causes marked inhibition of Na(+), K(+) ATPase activity [84]. Methylcitrate, itself, inhibits citrate synthase, aconitase, isocitrate dehydrogenase, and glutamate dehydrogenase activities, disturbs mitochondrial energy homeostasis, decreases ATP generation [42, 81, 85] and has been shown to cause morphologic changes and apoptosis of brain cells [43]. Thus, there is an energy deficit secondary to substrate insufficiency and toxin accumulation [86], as well as a direct impact on Krebs cycle intermediates resulting in secondary effects on other pathways [42, 44]. These inhibitory effects appear to explain some of the clinical signs seen in MMA and PROP, such as the hypoglycemia, lactic acidemia, hyperglycinemia, and hyperammonemia [17].

In addition, it has become increasingly evident that there is significant mitochondrial dysfunction, impairment of the oxidative phosphorylation system, increased production of reactive oxygen species (ROS), and increased

autophagy [30, 35, 42, 46, 59, 87–95]. The chronic effect of inhibition of mitochondrial energy production leads to oxidative stress, mitochondrial DNA damage, and altered mitochondrial morphology [44, 96]. The oxidative stress is mediated by increased levels of reactive oxygen species (ROS) and reduced ROS-protective levels of glutathione [44]. In addition, there are extensive mitochondrial ultrastructural changes in liver and kidney samples from MMA patients providing more evidence of mitochondrial dysfunction and respiratory chain impairment [59, 87, 89, 92, 97]. Mutase deficiency has been linked to mechanisms that cause mitophagy dysfunction and accumulation of damaged mitochondria that generate epithelial stress and tissue damage [87, 97]. Proteomic studies also suggest disturbances in proteins involved in energy metabolism, cellular detoxification, oxidative stress, cytoskeleton assembly, gluconeogenesis, and Kreb cycle anaplerosis [98, 99]. Finally, Storgaard et al. also suggested involvement of impaired lipolysis, blunted fatty acid oxidation, compensatory increase in carbohydrate utilization, and low work capacity as contributors to the pathophysiology of organic acidemias [100].

The etiology of the hyperammonemia seen in organic acidemias is different than that seen in urea cycle disorders. Recall that in the urea cycle, carbamoyl-phosphate synthesis is activated by N-acetylglutamate (NAG) [101]. Propionyl-CoA, which is accumulating in PROP, and isovaleryl-CoA, accumulating in IVA, are potent inhibitors of N-acetylglutamate synthase (NAGS) [11, 102]. Thus, NAG production is reduced and lack of NAG results in carbamoyl-phosphate synthetase inhibition and elevated ammonia concentrations [102]. It has also been suggested that hyperammonemia may be related to the inability to maintain adequate concentrations of glutamate precursors through a dysfunctional Krebs cycle secondary to accumulating methylcitrate and the decline in citric acid excretion [101].

18.4   Management

The goal of treatment of an individual with an organic acidemia is to reduce the accumulation of toxic metabolites, maintain normal growth, development, and nutritional status, prevent catabolism, and minimize complications [19, 44]. Therapy is multifaceted and typically involves a diet based on restriction of propiogenic amino acids, medication supplementation, and life-long monitoring [44]. Individualized dietary prescriptions, as prescribed by a metabolic nutritionist, balance the necessary intake of the restricted amino acids, other protein, and energy to provide the recommended daily allowances of nutrients and allow for adequate growth [103]. This is frequently accomplished by the use of special propiogenic amino acid-restricted medical foods combined with a prescribed amount of intact protein provided by breast milk or regular infant formula in infancy and regular solid foods in older children [19]. Provision of total protein intake modestly above the dietary reference intake (DRI) is well-tolerated and can provide a buffer against catabolism [32]. The target plasma range for restricted amino acids in PROP and MMA (isoleucine, valine, methionine, threonine) is low normal to normal [104]. In IVA, it is often sufficient to restrict natural protein to the recommended minimum daily requirements without the use of a leucine-free medical food [19, 104]. The target plasma range for leucine is 50–180 μM or normal range for the laboratory and 200–400 μM for glycine [104].

For all patients, particular attention must be paid to adequate energy intake. Energy requirements have been reported to be lower than predicted for age and sex during the well-fed state secondary to lower energy expenditure [105–107]. During illness, however, resting energy expenditure increases, requiring increased caloric intake to prevent catabolism and decompensation [19, 103]. These needs may require the use of additional fat and carbohydrate sources or protein-free modules. Catabolism is the major reason for acute decompensation [32]. If individual amino acids are found to be low, supplementation may be required, but no studies prove the efficiency of consistent supplementation of isoleucine and valine [107]. Nutrition management guidelines have been published by Yannicelli, Knerr et al., and Jurecki et al. [103, 104, 108] and are described in Chap. 21.

Therapy of IVA varies slightly from that of PROP and MMA. Isovaleryl-CoA conjugates

with glycine via the enzyme, glycine-N-acylase, forming isovalerylglycine, and also binds with carnitine, via carnitine N-acylase, to form isovalerylcarnitine [109, 110]. Both products, isovalerylglycine and isovalerylcarnitine, are easily excreted in the urine. This feature is exploited for both acute and chronic management. Thus, glycine (150–300 mg/kg/d) and carnitine (50–100 mg/kg/d) are both supplemented in individuals with IVA resulting in excretion of isovaleric acid [9, 11, 16, 19, 82, 83, 104, 109–114]. Subsequently, a strict metabolic diet may not be needed.

Supplementation of L-carnitine (100–400 mg/kg/d divided 2–3 times per day) is also an important aspect of the treatment of PROP and MMA [9, 19, 21, 32, 33, 103]. Provision of oral carnitine is effective in preventing carnitine depletion, regenerating the intracellular pool of free coenzyme A (CoA), and allows urinary excretion of propionylcarnitine, thereby reducing propionate toxicity [19, 104]. High doses of carnitine may cause a fishy odor due to overproduction of methylamines and may cause diarrhea [9, 103] but may be particularly helpful in PROP [32].

All patients with MMA should be tested for responsiveness to vitamin B_{12} [9, 19]. Testing regimes vary, but responsiveness can be determined by monitoring quantitative plasma or urine methylmalonic acid concentrations or by measuring metabolites via urine organic acid analysis. Vitamin B_{12} responsiveness leads to prompt and sustained decrease of propionyl-CoA byproducts [19]. Results should be confirmed by additional studies. Many vitamin B_{12}-responsive patients may need minimal to no protein or amino acid restriction [19]. In responsive patients, vitamin B_{12} is supplemented orally once per day or intramuscularly or subcutaneously daily or weekly with a beginning dose of 1 mg [19, 104]. A biotin responsive form of PROP has not been seen, but biotin dosed at 5–20 mg/d is sometimes supplemented in PROP [9, 32, 33, 103, 104].

As propionate production may result from gut bacteria, an intermittent antibiotic regime to reduce gut propionate production is sometimes implemented. The antibiotic, metronidazole, has been reported to be effective in reducing urinary excretion of propionate metabolites when used at a dose of 10–20 mg/kg once per day [16, 19, 103, 104]. The regime of therapy varies, but 7–10 consecutive days each month is a common practice [19, 33, 37, 104]. Some care providers prefer neomycin (50 mg/kg) because it is not absorbed [9]. Care must be taken to avoid complications associated with chronic antibiotic use including leukopenia, peripheral neuropathy, and pseudomembranous colitis. Metronidazole may also cause anorexia and dystonia [32, 103]. There are no studies that evaluate the clinical efficacy of metronidazole in improving clinical outcome, reducing ammonia concentrations, or reducing episodes of acute decompensation [32]. Overall, results of intermittent antibiotic use have been variable as measured by change in metabolite excretion, likely reflecting a variable colonization of gut bacteria by organisms which may or may not produce propionate [9].

Administration of N-carbamylglutamate (100–250 mg/kg/d) with or without ammonia scavengers has been suggested to help restore ureagenesis and improve acute hyperammonemia [18, 32, 44, 115, 116]. Increasing data is beginning to also suggest benefit of chronic use of N-carbamylglutamate (50 mg/kg/d) including a decrease in mean ammonia concentrations and a decrease in acute episodes of decompensation [44, 117]. Similarly, chronic therapy with sodium benzoate (150–250 mg/kg/d) has been proposed to help correct chronic hyperammonemia and hyperglycinemia [33]; however, there is no evidence that supports a role of sodium benzoate in chronic treatment especially given the evidence that higher glycine concentrations may be indicative of good metabolic control [32, 118]. Multivitamins may be given to reduce the risk of micronutrient deficiency. Citric acid and ornithine alpha-ketoglutarate have also been proposed to help sustain Krebs cycle flux and promote anaplerosis during illness and chronic management [96, 101, 119] with citric acid being most efficacious in one study of three agents [120]. In addition, coenzyme Q10 and vitamin E have been suggested as possible therapies for MMA-related optic neuropathy or secondary respiratory chain deficiency [46, 121, 122] and angiotension II inhibition has been suggested to help delay renal disease [123]. The role of growth hormone and supplemental alanine to promote anabolism has been suggested, but experience is

limited [9, 32, 124–126]. Glutathione deficiency treated with high doses of ascorbate has also been reported [127].

In addition, prompt treatment of intercurrent illnesses, particularly those placing the individual at risk for catabolism (e.g., vomiting, diarrhea, fever), and avoidance of fasting is paramount to reduce the risk of acute decompensations. Many children develop anorexia and feeding difficulties necessitating the placement of a gastrostomy tube to prevent fasting and ensure adequate dietary intake [33, 75, 128]. Patients and families should be provided an emergency medical letter as well as a sick day protocol [32]. A medical alert bracelet or necklace is also recommended [32].

Management of an acute decompensation involves reduction or discontinuation of protein and provision of energy to stop catabolism and promote anabolism by infusion of glucose and intralipid [21]. Fluid recommendations are standard for age. Using a 10% dextrose solution at 120–150 mL/kg/day (or 1.5 times maintenance) often can provide the necessary level of glucose delivery [37, 104]. Rehydration should occur over a 48-hour period to prevent cerebral edema [104]. Additional calories are added by using intralipid at 1–3 gm/kg/day [37, 104]. If hyperglycemia develops, an insulin drip (0.01–0.1 units/kg/h) may be necessary, but the dextrose delivery rate or amount should not be decreased [9, 37, 104]. Bicarbonate supplementation (1–2 mEq/kg) may be necessary to help correct acidosis [104]. If severe hyperammonemia is present, hemodialysis, hemofiltration, continuous chronic renal replacement (CCRT), extracorporeal membrane oxygenation (ECMO), and/or ammonia scavenging medications may be necessary [33, 37, 104, 129, 130]. Sodium benzoate and sodium phenylacetate, however, should be used with caution in patients with organic acidemias because glutamine concentrations can already be low and they may potentiate ammonia toxicity by blocking the urea cycle through sequestration of CoA [44, 115]. Carbamylglutamute (100–250 mg/kg/d) has been demonstrated to be beneficial in controlling the hyperammonemia associated with an acute

decompensation [33, 44, 102, 115, 131–135]. Administration of intravenous L-carnitine in relatively high doses (100–400 mg/kg/d) is used in acute illness [37, 104]. Metabolic decompensation in PROP may be complicated by hyperlacticacidemia due to thiamin deficiency, requiring supplementation (10 mg/kg/d) [104, 136, 137]. If the illness is prolonged, total parenteral nutrition may be necessary. Otherwise, reintroduction of protein occurs as tolerated, but should be reintroduced within 24–36 hours of therapy initiation [37, 104]. Frequent monitoring of laboratory studies and for possible complications is required.

For a fragile, medically intractable individual, liver, kidney, or combined liver kidney transplantation may be considered [138–148]. Transplantation is not a cure as it only partially corrects the enzymatic defect, but may result in improved survival, metabolic stability, neurologic function, and quality of life [32, 33, 86, 138–141, 149–155]. Perioperative complications, especially vascular complications, however, are common [138]. Liver transplantation has also been shown to improve cardiomyopathy [62, 156, 157], but cardiomyopathy has also recurred following transplantation [158]. Dietary therapy, perhaps liberalized, and L-carnitine supplementation are continued following transplantation [142, 145, 147, 149, 159]. Neurologic dysfunction, including metabolic stroke, and renal disease are not always prevented with transplantation [9, 17, 19, 32, 33, 160, 161]. One-year survival rate following transplantation was 72.2% in a multi-site, retrospective study of 12 individuals with PROP [32, 150] and may be up to 100% at experienced centers [138, 141, 162]. Therapies under investigation include import of transactivation of transcription (TAT) conjugated enzymes, viral vector-mediated gene transfer, systemic messenger RNA therapy, and genome editing [163–166].

18.5 Monitoring

Monitoring of patients with organic acidemias will vary according to each clinics' practice but should occur with some degree of regularity.

Patients should be seen routinely in clinic with routine monitoring of laboratory studies. Quantitative plasma amino acids should be obtained at least monthly in all patients managed with a restricted diet, although this practice varies between clinics. Quantitative methylmalonic acid is available in selected laboratories and may be used to follow individuals with MMA [9]. There is no established biomarker for monitoring therapeutic control in IVA [11]. Propionate concentrations may be difficult to obtain for individuals with PROP; some advocate following the methylcitrate to ctirate ratio via quantitative urine organic acid analysis or dried blood spots, if available [167, 168]. Propionylcarnitine has not been demonstrated to correlate with severity or level of control [32]. Ammonia, acid-base balance, and anion gap have been demonstrated to be important biochemical parameters in identifying an impending metabolic decompensation and to assess severity of PROP and MMA patients [169, 170]. The frequency of monitoring laboratory studies varies pending the patient's age and clinical stability. Laboratory studies to obtain every 6–12 months include complete blood count, complete metabolic panel (to include electrolytes, renal and liver function studies), carnitine, urinalysis, β-type natriuretic peptide, cystatin C, and calculated glomerular filtration rate, as well as annual nutrition monitoring studies to include prealbumin, 25-hydroxyvitamin D, vitamin B_{12}, iron, ferritin, and other micronutrients (thiamin, selenium) [32]. Additional laboratory studies to consider during acute illness include complete blood count, complete metabolic panel (to include electrolytes, renal and liver function studies), amylase, lipase, ammonia, osmolality, lactate, coagulation studies, creatine kinase, and urine ketones. Families can also be taught to test for urine ketones using ketone reagent strips at home as an early warning sign for pending decompensation [9] (Box 18.3).

Recent evidence suggests fibroblast growth factor 21 (FGF21) may be a predictive biomarker for metabolic stress in patients with MMA and PROP [171, 172]. The plasma concentrations of FGF21 appear to correlate with disease subtype and markers of mitochondrial dysfunction and

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Box 18.3: Laboratory Monitoring in Organic Acidemias[a]

- Routine:
  - Plasma amino acids
  - Prealbumin
  - Serum methylmalonic acid concentrations (MMA)
  - Urine Organic Acids
    - Urinary methylcitrate to citrate ratio (MC ≤ 2 times citrate in PROP)
- Annual
  - Complete blood count
  - Electrolytes, renal and liver function tests
  - Calculated creatinine clearance and glomerular filtration rate (GFR)
  - Carnitine (total, free and esterified)
  - Nutrient adequacy: vitamin D, B12, thiamin, iron studies, minerals (zinc, selenium)
  - β-type naturiuretic peptide
  - Urinalysis
  - Cystatin C
- Acute illness (additional)
  - Amylase, lipase, ammonia, ketones, lactate, coagulation studies, osmolality, CK

[a]Frequency depends on age of patient and clinical status, recommended monthly routine laboratory evaluations.

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are not affected by nutritional status or renal disease [171, 172]. Molema et al. suggested FGF21 levels >1500 during stable metabolic periods predicted an increase in long-term complications in patients with MMA and PROP [171]. This laboratory study, however, is not yet readily available for clinical use.

In addition to laboratory studies, management of an individual with an organic acidemia often requires the involvement of additional subspecialty services including neurology, nephrology, cardiology, neuropsychology, endocrinology, and ophthalmology. The utilization of these subspecialties is individualized to the clinical presenta-

tion of the patient. The patient may be seen yearly if monitoring is only required to assess increased risk or may be seen more frequently if organ system involvement is already noted [32]. Cardiology evaluation, however, with echocardiogram, ECG, and 24-hour Holter monitoring is recommended yearly in individuals with PROP [32] and MMA and during acute illnesses [27]. Schreiber et al. also recommended a baseline electroencephalogram and repeat studies as clinically indicated in all patients with PROP [35]. Long-term and repeated neuropsychological assessment is an excellent tool for tracking developmental progress or decline over time. Early evaluation and, if necessary, intervention are recommended beginning at a young age. Routine bone densitometry (DEXA scan) is also recommended for all patients typically beginning at age 5 years [27, 173]. Baseline endocrinology evaluation should be considered for female patients in late adolescence or thereafter. Nephrotoxic medications and medications that prolong the QT interval should be used with caution [27].

18.6 Summary

The outcome of individuals with organic acidemias is quite variable. In general for PROP and MMA, late onset forms appear to have a better prognosis as compared with early onset forms, mut$^-$ MMA patients appear to do better than mut^0 patients, and individuals with vitamin B_{12} responsive MMA appear to have improved outcome over patients with vitamin B_{12} unresponsive forms [10, 21, 34, 40, 58, 128, 174, 175]. In MMA, an earlier age of onset, the presence of hyperammonemia at diagnosis, and a history of seizures also predict more severe impairment [176]. The duration of hyperammonemia, abnormal acid–base balance with metabolic acidosis, and coma correlate with poor neurologic outcome [44]. Also, in general, individuals with IVA appear to have a better outcome than those with MMA or PROP; however, in contrast to MMA and PROP, the neurocognitive outcome in patients with a neonatal presentation is more favorable than in patients with a late diagnosis

[177, 178]. Mortality has been reported to be >80% in the neonatal onset form of these disorders and as high as 40% before 16 years of age in the late onset forms [33, 179]. Survival has improved [33]. The survival at one year of age in patients with mut^0 was 65% in the 1970s but has increased up to 90% in the 1990s [17]. Death may be due to cerebral edema, cerebral or cerebellar hemorrhage, infection, renal failure, heart failure, arrhythmias, cardiomyopathy, pancreatitis, or irreversible metabolic decompensation [9, 51, 63, 68, 179–181].

Morbidity is also high with frequent complications, poor growth and nutritional status, poor neurodevelopmental progress with frequent progressive neurocognitive deterioration, abnormal neurologic signs such as chorea and dystonia, and frequent and severe relapses of metabolic decompensation [6, 10, 21, 33, 68]. Overall, developmental outcome is poor in PROP and MMA with the majority of patients demonstrating developmental delay [6, 33, 51, 68, 75, 86, 178]. Martin-Hernandez et al. reported on the long-term needs of adult patients with organic acidemias [40]. In this series of 15 patients, largely with late onset disease, two-thirds of the patients had neurologic or visceral complications, and three-quarters of them required some kind of social support [40]. In contrast, developmental outcome in IVA is normal in 60% or more of the patients [86, 178]. In addition, long-term complications and the risk of metabolic decompensations associated with catabolic stress in individuals with IVA are also much less frequent than compared to PROP and MMA [40, 178]. Evaluation of older patients is beginning to suggest a risk of psychiatric disorders [86].

Outcome and prognosis, however, may be changing and improving with early identification via newborn screening. A benign MMA phenotype has been described and some patients with MMA have remained symptom-free [4, 182, 183]. In addition, infants diagnosed with IVA by newborn screen have also remained asymptomatic with carnitine supplementation and mild or no dietary restriction and retrospectively identified siblings ranging in age from 3 to 11 years were also asymptomatic [7, 11]. Dionisi-Vici

et al. compared the outcome of 29 patients with MMA, PROP, or IVA diagnosed clinically to 18 similar patients diagnosed by newborn screening. The newborn screened population demonstrated an earlier diagnosis, significantly reduced mortality (11% compared to 51%) and an increased number of patients with normal development at <1 year of age [10]. A more stable clinical course with less frequent relapses of decompensation was also demonstrated [10]. Similar findings were also found by Grünert et al. in a population of patients with PROP, however, they did not demonstrate a reduction of complications in patients diagnosed by newborn screening [184]. Overall, newborn screening and early diagnosis may result in decreased early mortality, decrease severity of initial symptoms, and improved neurodevelopmental outcome [10]. Outcome data, however, is early and limited and more long-term follow-up studies are needed.

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