HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Curr Opin Pediatr. 2016 December ; 28(6): 682–693. doi:10.1097/MOP.0000000000000422.

Methylmalonic and Propionic Acidemias: Clinical Management Update

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Abstract

Purpose of review—Recent clinical studies and management guidelines for the treatment of the organic acidopathies methylmalonic acidemia (MMA) and propionic acidemia (PA) address the scope of interventions to maximize health and quality of life. Unfortunately, these disorders continue to cause significant morbidity and mortality due to acute and chronic systemic and end-organ injury.

Recent findings—Dietary management with medical foods has been a mainstay of therapy for decades, yet well controlled patients can manifest growth, development, cardiac, ophthalmological, renal and neurological complications. Patients with organic acidopathies suffer metabolic brain injury which targets specific regions of the basal ganglia in a distinctive pattern, and these injuries may occur even with optimal management during metabolic stress. Liver transplantation has improved quality of life and metabolic stability, yet transplantation in this population does not entirely prevent brain injury or the development of optic neuropathy and cardiac disease.

Summary—Management guidelines should identify necessary screening for patients with MMA and PA, and improve anticipatory management of progressive end-organ disease. Liver transplantation improves overall metabolic control, but injury to non-regenerative tissues may not be mitigated. Continued use of medical foods in these patients requires prospective studies to demonstrate evidence of benefit in a controlled manner.

Keywords

methylmalonic acidemia; propionic acidemia; brain injury; liver transplantation; medical foods

Introduction

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are rare, autosomal recessive, multisystemic inborn errors of branched chain amino acid metabolism which cause

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Conflicts of interest

The authors have no conflicts of interest to report.

significant morbidity and mortality in infancy and childhood, and, for survivors, significant debilitating end-organ damage into adulthood. MMA and PA, as organic acidopathies (OAs), result in defective mitochondrial metabolism of coenzyme A (coA)-activated carboxylic acids, which are largely derived from the metabolism of branched-chain amino acids, odd-chain fatty acids, and cholesterol. Clinical features of OAs may occur due to accumulation of toxic metabolites, altered mitochondrial energy metabolism, carnitine depletion, and coenzyme A sequestration. Acute illness may be associated with metabolic acidosis, acute alterations of consciousness or encephalopathy, anorexia, and nausea and vomiting [1, 2]. Chronic complications include poor growth, movement disorders, progressive spastic quadraparesis, epilepsy, cardiac dysfunction (PA>MMA), progressive renal disease (MMA), osteopenia/osteoporosis, vision loss (MMA>PA), and functional immunodeficiency [1, 3–35]. Recent investigation into the pathophysiology of the end-organ effects seen in patients with OAs has improved screening for disease related complications, and recent treatment recommendations are the first steps toward standardization of care [36].

Clinical Presentation, Diagnosis, and Management

PA and MMA classically present in a term neonate within the first 3 days of life, who feeds poorly, is pancytopenic, becomes progressively encephalopathic, and ultimately progresses to coma and death without prompt identification and management [22, 37–44]. The differential diagnosis in this age group includes sepsis, hypoxic-ischemic encephalopathy, drug intoxication (from maternal exposure before and/or during delivery), and other inborn errors of metabolism. Sick neonates who appear septic or encephalopathic with an anion gap metabolic acidosis, ketoacidosis, lactic acidosis, hyperammonemia, and/or hypoglycemia should be stabilized expectantly with reversal of catabolism using dextrose containing fluids with a glucose infusion rate of 6–8 mg/kg/min, with intralipids at 2–3 grams/kg/day, while removing all source of protein from the infant. Workup for intoxication-type inborn errors of metabolism (IEM) should occur immediately upon clinical indication and include blood gas (non-capillary), comprehensive metabolic panel, complete blood count, blood culture, urinalysis (specifically for urine ketones, which should be negative in a healthy newborn without and IEM), lactate, ammonia, urine organic acids, plasma amino acids, and an acylcarnitine profile [45].

Once the infant is acutely stabilized and diagnosed, lifelong aggressive management by metabolic physicians remains essential. Despite management based on best practices, including dietary protein restriction, carnitine supplementation, and the use of drugs to modulate ammonia, these patients frequently experience acute metabolic decompensation during acute illness or other stressors such as surgical or interventional procedures [1, 45–58]. In older patients with the classical OAs, acute decompensation events continue, frequently due viral illness or surgical procedures. Frequently, these patients will have significant complications due their disease, discussed below.

Patients with milder variants of isolated MMA (*mut*$^{-}$, or the cobalamin disorders Cobalamin A (*cblA*) or B (*cblB*), which result in deficiency of the adenosylcobalamin cofactor for MUT) or PA may not present until later in infancy, childhood, or adolescence. While the definition of early versus late onset remains controversial within the OAs, Heringer et al

classify late-onset disease as any patient in whom the first clinical symptoms occur outside of the neonatal (first 30 days of life) period, although some patients may not present until much later in life [59]. In patients who were not diagnosed by expanded newborn metabolic screening (NMS), Heringer and colleagues report that for MMA and PA, the median age at onset of clinical symptoms was 6–8 days in the early-onset group, while in the late-onset group, the median age at diagnosis was 210–348 days. Approximately half of the non-NMS MMA and PA cohort were classified as late-onset, but most of these diagnoses occurred during infancy [59]. In MMA, these childhood and adolescent-onset patients may present with chronic renal failure, and evaluation for MMA should occur in all patients who present with progressive proximal tubular renal dysfunction [60–64]. Late-stage presentation of PA may include seemingly isolated cardiomyopathy, while patients with PA and MMA may present with progressive spastic quadraparesis, progressive movement disorder, or vision loss [6, 7, 14, 32, 33, 35, 58, 65–71]. Some patients who self-restrict protein due limited protein tolerance may present later in life with metabolic decompensation or metabolic stroke following a surgical or interventional procedure where fasting for several hours is required. Additional complications of later-onset MMA and PA are similar to those with classical disease and are discussed below.

Diagnosis

Diagnosis typically occurs during an initial decompensation event in the neonatal period, which may resemble neonatal sepsis and present with poor feeding, vomiting, lethargy, and progression to coma and death without prompt and effective therapy. Diagnosis is based on clinical presentation and laboratory analysis, metabolic acidosis, ketoacidosis, lactic acidosis, hyperammonemia, hypoglycemia, pancytopenia, and elevated C3 acylcarnitines and organic acids in the urine. Metabolites elevated in PA include elevated plasma propionylcarnitine, glycine, and alanine, and elevated urinary 3-OH-propionate and methylcitrate [72–85]. In MMA, elevations of plasma propionylcarnitine, glycine, and alanine coupled with elevation of urinary methylmalonic, 3-OH-propionic, and methylcitric acids provide the diagnosis [72–78, 86–88].

Some infants, however, are detected based on NMS prior to a decompensation event. A recent study of organic acidemia outcomes using compiled data from the European registry and network for intoxication type metabolic diseases (E-IMD) demonstrates that, for infants diagnosed with OAs on newborn screening, 52% with cobalamin non-responsive MMA, 67% with cobalamin responsive MMA, and 49% with PA were asymptomatic at 8 days of life [59]. OA patients detected by expanded NMS are somewhat more likely to have normal development of motor milestones and less likely to have a movement disorder, although movement disorders and metabolic brain injury may occur at any age, and the median age of subjects in this study were under 10 years of age [59]. Furthermore, other neurological and neurocognitive outcomes were not explored, and thus, in spite of earlier detection, these patients are likely to develop some degree of neurological sequela of disease, and other end-organ sequelae have not been analyzed in this cohort.

Defects in other genes within the propionate catabolism pathway or mitochondrial disorders may also result in excretion of methylmalonic acid in the urine [89, 90]. These disorders are

rarer than classical isolated MMA, often manifest other biochemically diagnostic markers in urine or plasma to suggest the diagnosis, and will not be addressed further in this review.

Biochemical Perturbations in PA and MMA

Mutations in the *PCCA* and *PCCB* genes cause PA by generating defective or absent propionyl-CoA Carboxylase (PCC), which is biochemically upstream of MUT [91–130]. Isolated MMA is caused by mutations in the *MUT* gene encoding methylmalonyl-CoA mutase (mut) or the genes encoding the enzymes responsible for the generation of 5-deoxyadenosylcobalamin (AdoCbl) cofactor of Mut (*MMAA* and *MMAB*) (Fig. 1)[131–148]. The subtypes of MMA are based on complementation subclasses and include *mut*, *cblA*, and *cblB*, based on the enzymatic cause of the condition[149]. Mut deficiency may be further divided into subclasses based on the degree of enzymatic activity of the mutase enzyme, designated mut^0, for enzymes with null activity, and mut^- for enzymes with reduced or minimal activity[141]. Other causes of isolated MMA include much rarer deficiencies in other enzymes within the propionate catabolism pathway or in other components of mitochondrial function.

With normal enzymatic function, propiogenic precursors are converted sequentially from propionyl-CoA to methylmalonyl-CoA to succinyl-CoA, which is subsequently metabolized within the TCA cycle [131, 132, 150–152]. This complex role of PCC and MUT within mitochondrial energy metabolism mirrors the biochemical and clinical findings associated with OA disease [153–159]. Approximately two-thirds of normal propiogenic load is generated from dietary intake and muscle turnover, while around one-third naturally originates from gut bacterial sources [160, 161]. During decompensation, acidosis in these patients occurs due to accumulation of organic acids and ketoacids, while lactic acidosis also occurs, particularly in severe decompensation or with severe secondary mitochondrial dysfunction [61, 162–166]. Accumulation of propionyl-CoA, and to some extent methylmalonyl-CoA, results in secondary inhibition of N-acetylglutamate synthase (NAGS), causing secondary hyperammonemia in these patients [167–170]. Generation of propionylcarnitine moieties may result in cardiac arrhythmias and cardiomyopathy due to secondary carnitine deficiency [29, 171].

Complications and Management of MMA and PA

Because normal mitochondrial function requires sufficient energy production through the citric acid cycle and oxidative phosphorylation, MMA and PA result in multi-systemic chronic disease, particularly in the highly energetic organs such as brain, heart, kidney, and eye. End-organ injury occurs due to both primary toxicity of both the accumulating primary and secondary metabolites and deficiency of succinyl-CoA resulting in Kreb cycle and oxidative phosphorylation dysfunction. Periods of acute illness frequently chronically worsen the patient's basal condition due to increased energetic dysfunction.

Dietary Management

In the well state, OA patients are typically maintained on a protein-limited diet, or if enteral gastric feedings are required, combinations of standard, age-appropriate enteral formulas with formulas specially-designed for OA patients may be employed. While protein restriction is more aggressive in patients with other inborn errors of metabolism, in OAs dietary protein intake should target the recommended daily allowance for protein (0.8 grams protein/kg body weight), unless differences based on the individual patient response require lower or higher concentrations. Patients with spasticity or severe choreoathetosis may require additional protein nutrition for their increased energetic demand, and other patients with brittle, difficult to manage disease may require less whole protein and, based on clinician preference, addition of medical foods or formulas [12, 53, 172–179]. The primary dietary goal in OA patients should remain prevention of catabolism and allow normal growth, without causing obesity. Thus, providing sufficient protein, preferably from natural protein sources with as little amino acid-deficient protein from medical foods as possible, is preferred. Recently, dietary analysis of a large cohort of patients has revealed that patients with MMA typically tolerate the recommended daily allowance of protein. However, many of these patients were receiving a large proportion of protein from propiogenic-deficient sources and were also noted to have poor growth in height and weight, elevated leucine levels, and low levels of isoleucine and valine, often requiring specific amino acid supplementation [180]. Prior patients on such diets developed severe amino acid deficiencies [176, 178]. Thus, the use of medical foods deficient in propiogenic precursors appears to result in branched chain amino acid deficiencies and may worsen outcomes. Therefore, coordination with a metabolic dietician is strongly recommended to ensure that nutritional and amino acid deficiencies are prevented, and future prospective studies on the safety and efficacy of medical foods for OAs should occur to ensure that iatrogenic secondary effects are prevented in this already vulnerable population.

Medical Management

Patients with PA and MMA require carnitine supplementation to prevent secondary carnitine deficiency (L-carnitine, enterally administered at 50–100mg/kg/day), and those patients with B12 responsive MMA, usually cblA disease, should receive daily injections of hydroxocobalamin (1 mg, intramuscularly every day) [12, 57, 144, 145, 181, 182]. Some patients are treated with cycles of enteral antibiotics (metronidazole) to reduce the burden of propiogenic gut flora [36, 161, 173, 183]. Some brittle patients with chronic hyperammonemia may be treated orally with sodium benzoate or sodium phenylbutyrate (Buphenyl) at 10 grams/m^2/day, with careful monitoring of amino acid levels and electrolytes [12, 36]. This is not a standardized practice, but may be instituted by a metabolic physician based on professional experience and provider preference.

Acute Metabolic Decompensation

Patients with OAs may become very ill from otherwise mild viral illnesses, and other events that cause physical or emotional stress may trigger catabolism, including surgical procedures, labor and childbirth, and abrupt changes in nutritional status. Aggressive acute

management of intercurrent illness and mitigation of other stressors must be undertaken to limit the degree of decompensation and sequelae from these events. Limited reports indicate that patients with PA and MMA may not maintain sufficient humoral immune response to combat viral infection [184, 185]. Reversal of catabolism, promotion of anabolism and identification and treatment of the underlying precipitating etiology are paramount to management of the acute decompensation.

With intercurrent illness, PA and MMA patients typically present with nausea and vomiting, worsening anorexia, and encephalopathy, with laboratory studies demonstrating metabolic acidosis, ketonuria, hyperammonemia, pancytopenia, and electrolyte disturbances [1, 22, 45, 86]. These decompensation events typically present with decreased oral intake or enteral feeding intolerance, vomiting, and altered mental status or lethargy. Without aggressive reversal of catabolism with intravenous dextrose-containing fluids (typically 10–12.5% dextrose in normal saline with appropriate electrolyte additives at 150% of maintenance, unless renal function demands different electrolyte composition or volume), patients with OAs may die or suffer severe metabolic brain injury [22, 36, 45]. Some providers choose to employ intralipid in addition to dextrose fluids for additional caloric support [36, 45]. In addition to reversal of catabolism, more aggressive metabolic therapies are employed during decompensation, including ammonia scavenging with sodium phenylacetate-sodium benzoate (Ammonul, intravenous preferably via central line, variable dosing based on age/weight) or disinhibiton of urea cycle function by N-carbamylglutamate (Carbaglu, oral, 100 mg/kg bolus followed by 25–62 mg/kg every 6 hours, currently under investigational status with the United States Food and Drug Administration) [36, 45, 186–189]. The ammonia scavengers allow conjugation of amino acids to the scavenger compounds to bypass the urea cycle and permit excretion [39, 159, 190, 191]. Inhibition of carbamylphosphate synthetase I (CPS1), a urea cycle enzyme, by accumulating metabolites in OAs causes secondary hyperammonemia in these disorders [167]. N-carbamylglutamate, an N-acetylglutamate analogue, allosterically activates CPS1 and inhibits the secondary effects of the propionate metabolites on CPS1 [36, 45, 189, 192–195]. Once catabolism has been reversed and acidosis corrected, complete nutrition should be reinitiated as soon as possible, preferably via the enteral route. Once the precipitating source is identified and treated or managed, the patient may be transitioned back to standard diet.

Chronic Management and Screening Recommendations

Optimal management of individuals with MMA and PA includes careful dietary management and regular screening for known complications of the OAs [12, 22, 36, 57]. Table 1 catalogues the most common complications associated with PA and MMA and the recommendations for screening and management. Metabolic “strokes”, frequently indicated by significant acute mental status changes or new or worsening abnormal movements, require immediate laboratory and imaging evaluation and reversal of catabolism [12, 17, 22, 34, 65–67, 196–198]. Once dextrose-containing intravenous fluids and treatment of the underlying precipitant are initiated, MRI and magnetic resonance spectroscopy may be performed to evaluate the location and extent of evolving injury [17, 66, 199–202]. Movement disorders or spastic quadra- or paraparesis, potential sequelae of metabolic strokes, should be managed in collaboration with a neurologist and/or physiatrist to allow for

optimal function and minimum disability. If spasticity or movement disorder worsens and limits the patient's ability to perform activities of daily living, referral to speech, physical, and/or occupational therapy should occur [203].

Patients with PA and, less commonly, MMA may develop life-threatening cardiac arrhythmias, particularly prolonged QTc, or cardiomyopathy, with or without carnitine deficiency [4, 12, 28, 204, 205]. All individuals should be routinely screened with echocardiography and EKG yearly, during admissions for illness (EKG), or with cardiac symptoms [12, 36]. Medications that prolong the QT interval should be used with caution in OA patients and avoided to the extent possible in patients with known cardiac disease. All patients who are hospitalized for metabolic decompensation or due to an invasive or surgical procedure should be placed on telemetry to monitor for life-threatening arrhythmias during these crises.

The significant ophthalmological effects of MMA and PA require close collaboration with an ophthalmologist comfortable with managing the retinal and optic nerve degeneration associated with associated with these diseases [6, 7, 14, 35, 70, 206–209]. While effective ophthalmic therapies remain elusive, careful monitoring for vision loss and provision of support services are vital for maintaining patient function. As ophthalmological innovations occur for retinal and optic nerve disease, MMA and PA patients with access to an ophthalmologist may benefit from trials with new devices and therapies.

MMA frequently, and PA rarely, result in progressive, severe renal disease, often requiring transplant, [8, 61–64, 210–216]. Patients with MMA and PA should be carefully screened with laboratory markers of renal function including BUN and creatinine, which are frequently near normal until late stage disease, as well as calculated creatinine clearance or glomerular filtration rates, and cystatin C. Other markers of renal function, including erythropoietin and 1,25-hydroxy vitamin D in the setting of appropriate vitamin D intake/supplementation may indicate additional investigation for worsening renal disease. Patients with indications of declining renal function require referral to a nephrologist for further evaluation and management, as dialysis and/or renal transplantation may become necessary, particularly in adolescents and adults with MMA. Nephrotoxic medications should also be avoided or limited in these patients.

Although the specific mechanisms associated with bone health in OAs remain incompletely investigated, patients with PA and MMA are at significantly increased risk for osteopenia or osteoporosis that their age-matched peers, with and without renal disease [22, 41]. DXA scan evaluation should be performed routinely starting at age 5, the earliest age for which height, race, and gender adjustment norms exist, and radiographic evaluation for fractures in patients presenting with pain should always be considered. Various pathologies including vertebral fusion anomalies, vertebral compression and fractures, as well as generalized osteopenia, have been observed. Therapeutic intervention should address morbidity associated with such low BMD, and the use of bisphosphonates versus calcitriol to target anti-resorption versus anabolic measures to support increased deposition is dependent on the individual patient's findings (BMD, bone age, parathyroid hormone, 1,25-OH and 25-OH vitamin D levels, sex hormone production), and even bone biopsy should be considered for

responsiveness to bisphosphonates prior to their initiation. If pathological fractures or significant osteopenia/osteoporosis are detected on screening, more robust monitoring for bone density and response to interventions are indicated. Currently, further studies are required to determine the role of medical food use, renal disease, or other contributing factors such as immobility or metabolic fragility in the development of low bone mineral density.

Transplant

Some individuals have received liver transplants to treat PA and liver, kidney, or combined liver-kidney to metabolically stabilize MMA and/or address the chronic renal failure associated with MMA disease [12, 18, 24, 60, 196, 201, 217–239]. Liver transplantation has become an increasingly popular treatment choice for children with more severe or brittle disease, and some adults undergo isolated kidney transplant for MMA-related end-stage renal disease. For adolescents, however, combined liver and kidney transplant has also been employed in MMA. Liver transplantation does improve the metabolic stability of brittle OA patients, and some sequelae may be mitigated, including cardiomyopathy. One center has claimed that liver transplantation is more cost-effective than dietary therapy alone [228]. Not all sequelae of PA and MMA may be prevented by liver transplantation; some liver-transplanted patients have developed metabolic stroke after transplant and others have had progressive vision loss due to optic atrophy as well [18, 231, 232, 236, 239, 240]. Further studies on the long-term outcomes of transplantation and changes to the natural history of disease are indicated.

Conclusions

For patients with PA and MMA who survive their initial decompensation episode, significant morbidity remains a lifelong threat. Better therapies for these disorders remain elusive, but a critical mass of patients has now contributed to our understanding of the natural history of these diseases. Most importantly, recently proposed diagnostic and management guidelines have emerged from worldwide experts in these disorders and should improve management of these patients. Dietary management of the OAs should receive additional scrutiny in the near future with prospective, controlled studies to demonstrate the optimal circumstances for the use of medical foods and improvements in formulations of these foods to prevent iatrogenic morbidity. Better understanding of the pathophysiology of metabolic brain injury in the OAs must occur to permit further drug targeting for neuroprotection and recovery from metabolic insult. Finally, the use of orthotopic liver transplantation to improve metabolic stability in patients with OAs is burgeoning and will likely change the natural history of these disorders, yet we must ensure our patients’ families understand the limitations of this therapy, including ongoing risk to the CNS compartment following transplantation and the inherent risks of liver transplantation.

Acknowledgments

Funding Sources: Child Health Research Career Development Award (Fraser), Intramural Research Funding – NHGRI (Venditti)

Financial support and sponsorship

This work was supported by the Intramural Research Program of the National Human Genome Research Institute (CPV) and the Child Health Research Career Development Award (K12) via Children's National Medical Center (JLF).

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Key Points

- Diagnostic and management guidelines for PA and MMA are emerging and may improve long-term care.
- Prospective, controlled studies are needed to support the use of medical foods and their formulations to limit iatrogenic morbidity in PA and MMA.
- The pathophysiology of metabolic brain injury in the OAs requires further elucidation to permit future drug targeting for neuroprotection and recovery.
- Orthotopic liver transplantation improves metabolic stability in patients with OAs and will likely change the natural history of these disorders, but is not curative.

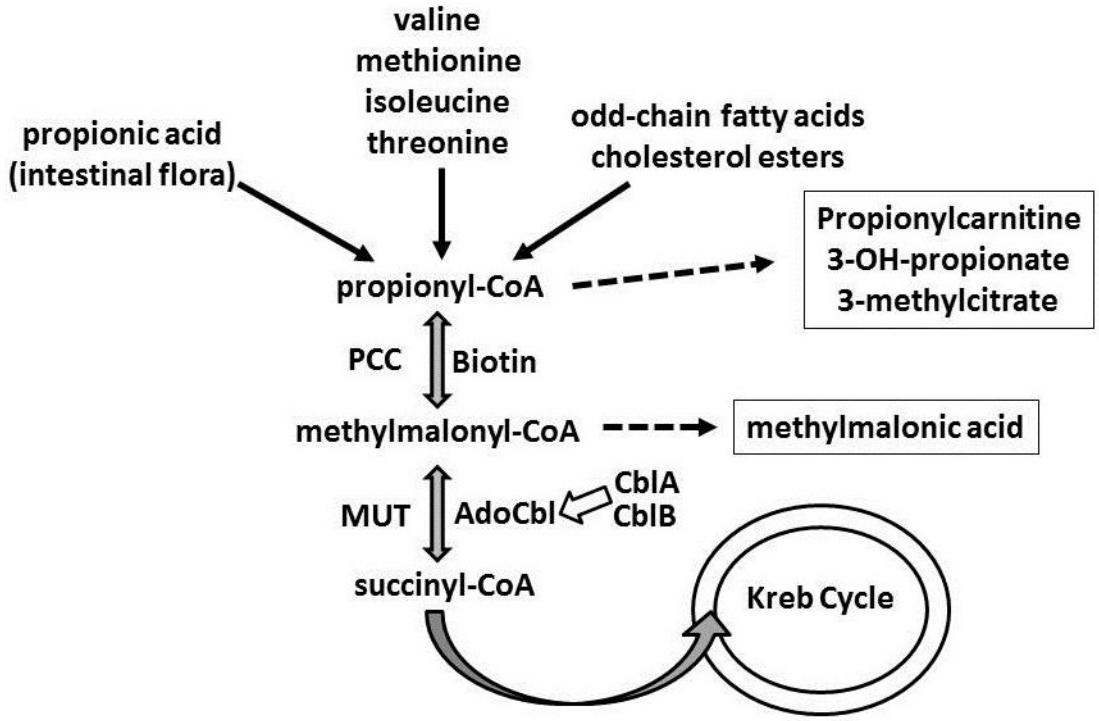

Figure 1.

Biochemical Pathway of Propionate Metabolism. For simplification, the methylmalonyl-CoA epimerase enzyme step has been removed from the pathway diagram. AdoCbl: adenosylcobalamin, CblA: Cobalamin A, CblB: Cobalamin B, MUT: methylmalonyl-CoA mutase, PCC: propionyl coA carboxylase.

Table 1

Chronic Manifestations and Management of PA and MMA

Organ System	Manifestations	PA	MMA	Evaluation and Management
Constitutional	Failure to thrive	++	++	Consider need for gastrostomy tube placement to permit sufficient caloric intake.
	Anorexia	++	++	
	Feeding difficulty	++	++	
CNS	Movement Disorder Spastic quadra-/para-paresis (progressive)	++	++	Neurological evaluation and treatment of movement disorders and spasticity.
	Metabolic “stroke” involving basal ganglia	++	++	MRI with spectroscopy to evaluate prior injury and acute/evolving injury in symptomatic patients. Reversal of catabolism.
	Variable intellectual disability	++	+	Ensure appropriate legal documentation in place for power of attorney, guardianship, etc. as indicated based on level of functioning.
Ophthalmological	Optic nerve atrophy Retinal degeneration	+	++	Routine ophthalmological evaluation and treatment at regular intervals.
Gastrointestinal	Pancreatitis	++	+	Monitoring of pancreatic enzyme levels with illness and adjustment of feeding paradigm as indicated.
Renal	Tubulointerstitial nephritis	−	++	Routine screening of clinically available markers for renal disease. GFR preferable.
	Chronic Progressive Renal Failure	+	++	Avoid/limit/renally dose nephrotoxic medications in patients with evidence of declining renal function.
	End Stage Renal Disease	+	++	Evaluation for organic acidopathies in patients with renal failure of unknown cause with suggestive history.
Cardiovascular	Arrhythmias, including prolonged QTc	++	+	Telemetry for arrhythmias and prolongation of QT interval.
		++	+	Cardiology evaluation with echocardiography and EKG yearly or with symptoms.
	Cardiomyopathy	++	+	
	Heart Failure	+	−	Concurrent management with cardiology for cardiac pathology.
Skeletal	Osteopenia/Osteoporosis	+	+	Routine screening with DXA every 5 years.
	Pathological Fractures		+	Routine (yearly) monitoring, consider addition of bisphosphonates.