Received: 13 February 2019 | Revised: 18 May 2019 | Accepted: 21 May 2019

DOI: 10.1002/jimd.12129

REVIEW ARTICLE

JIMD SSIEM WILEY

Pathophysiology of propionic and methylmalonic acidemias. Part 1: Complications

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Communicating Editor: Piero Rinaldo

Funding information
Alexandre Suerman Stipend from the University Medical Centre Utrecht (H.A. Haijes) (in line with JIMD12128)

Abstract

Over the last decades, advances in clinical care for patients suffering from propionic acidemia (PA) and isolated methylmalonic acidemia (MMA) have resulted in improved survival. These advances were possible thanks to new pathophysiological insights. However, patients may still suffer from devastating complications which largely determine the unsatisfying overall outcome. To optimize our treatment strategies, better insight in the pathophysiology of complications is needed. Here, we perform a systematic data-analysis of cohort studies and case-reports on PA and MMA. For each of the prevalent and rare complications, we summarize the current hypotheses and evidence for the underlying pathophysiology of that complication. A common hypothesis on pathophysiology of many of these complications is that mitochondrial impairment plays a major role. Assuming that complications in which mitochondrial impairment may play a role are overrepresented in monogenic mitochondrial diseases and, conversely, that complications in which mitochondrial impairment does not play a role are underrepresented in mitochondrial disease, we studied the occurrence of the complications in PA and MMA in mitochondrial and other monogenic diseases, using data provided by the Human Phenotype Ontology. Lastly, we combined this with evidence from literature to draw conclusions on the possible role of mitochondrial impairment in each complication. Altogether, this review provides a comprehensive overview on what we, to date, do and do not understand about pathophysiology of complications occurring in PA and MMA and about the role of mitochondrial impairment herein.

KEYWORDS

complications, methylmalonic acidemia, pathophysiology, propionic acidemia

Abbreviations: BMD, bone mineral density; HPO, human ohenotype ontology; MCM, methylmalonyl-CoA mutase; MMA, isolated methylmalonic acidemia/aciduria; NMDA, *N*-methyl-D-aspartate; PA, propionic acidemia/aciduria; ROS, reactive oxygen species.

Nanda M. Verhoeven-Duif and Peter M. van Hasselt contributed equally to this study.

1 | INTRODUCTION

Over the last decades, advances in clinical care for patients suffering from branched-chain organic acidemias like propionic acidemia (PA) and isolated methylmalonic

acidemia (MMA) have resulted in improved survival. These advances were based on new insights in pathophysiology. The understanding that both diseases are caused by an enzyme deficiency in the breakdown of branched-chain amino acids resulted in the implementation of a protein restricted diet.[1,2] In addition, the recognition that MMA is caused by a deficiency of an enzyme for which cobalamin is a cofactor paved the way to cobalamin supplementation[3] and the understanding that carnitine acts as a scavenger for the toxic metabolites produced in PA and MMA led to the introduction of carnitine supplementation.[4] By virtue of these therapies—and general advances in clinical care—patients now tend to reach adulthood. However, it is increasingly recognized that residual disease in these disorders is substantial. Quite frequently, devastating complications may occur suddenly. These complications largely determine the unsatisfying overall outcome of patients. Current treatment strategies are thus inadequate for prevention and treatment of many complications in PA and MMA. To improve outcome, we need to optimize treatment, for which we have to gain insight in the pathophysiology of complications.

For this review we performed a systematic data-analysis of cohort studies and case-reports on PA and MMA to identify common denominators in the hypotheses on pathophysiology of complications occurring in PA and MMA. A broad PubMed literature search resulted in 2176 records. A total of 181 publications were included based on full text, including 20 cohort studies, 34 studies on brain imaging, 16 studies on kidney failure, 12 studies on cardiomyopathy and 99 other case-series and reports covering a wide range of complications occurring in PA and MMA (Supporting Information, Figure S1). For each of the frequent complications in PA and MMA that have been assessed in cohort studies we extracted the prevalence of the complication, and for each of the rare complications that have been described in case-reports, we extracted the number of patients reported with

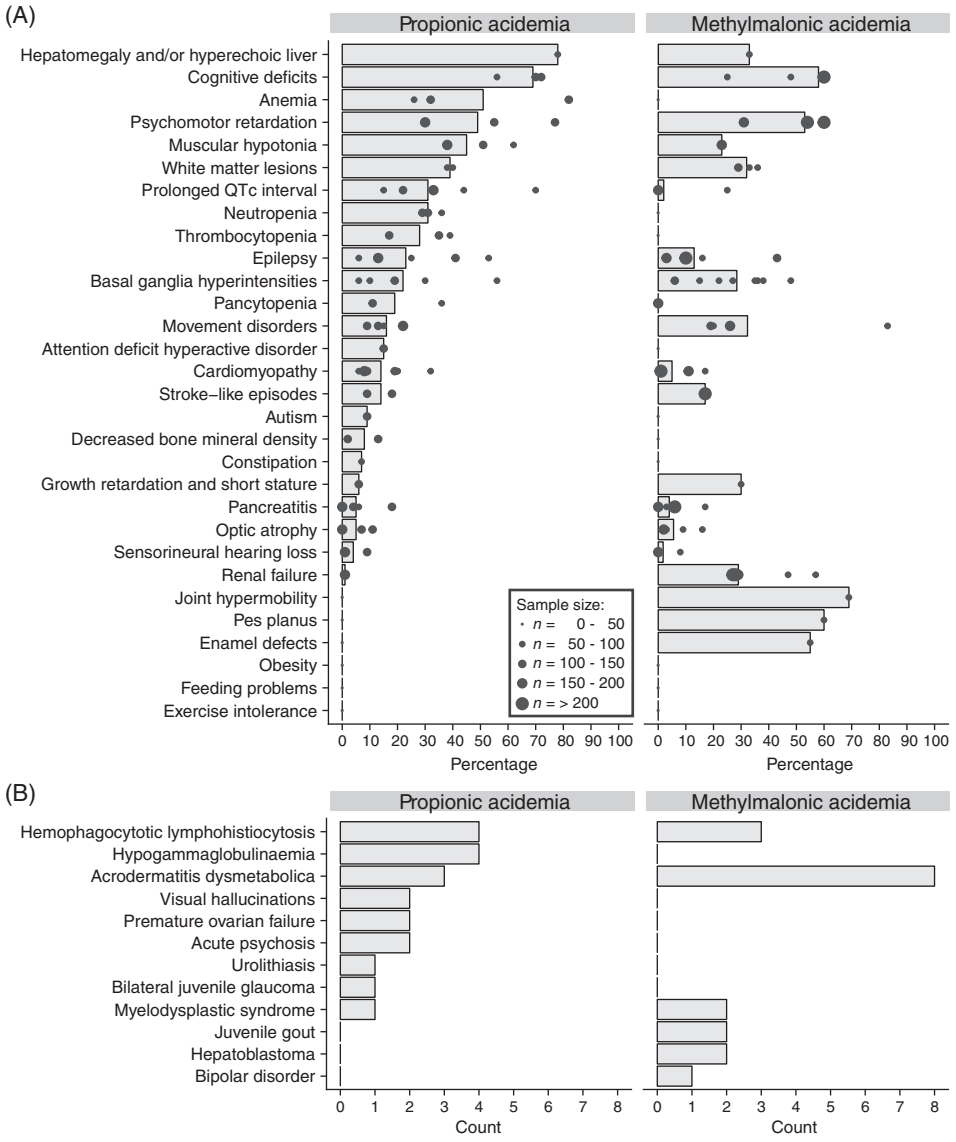

FIGURE 1 Prevalence of complications occurring in PA and MMA. A, Complications are listed on the *y*-axis. The *x*-axis depicts the percentage in either propionic acidemia (PA) or methylmalonic acidemia (MMA). Dark-gray dots depict the percentages reported in the different cohort studies, the size of the dot indicating the sample size of the study. Light-gray bars depict the sample size-weighted percentage. B, Complications are listed on the *y*-axis. The *x*-axis depicts the number of patients with either propionic acidemia (PA) or methylmalonic acidemia (MMA) that were reported to have this complication, indicated by the light gray bars

that complication (Figure 1). Furthermore, we summarized the current hypotheses and evidence for the underlying pathophysiology of each reported complication.

A common hypothesis on pathophysiology of many complications is that mitochondrial impairment plays a major role. We assumed that these mitochondria associated complications are overrepresented in monogenic mitochondrial diseases and, conversely, that complications in which mitochondrial impairment does not play a role are underrepresented in mitochondrial disease. We studied, for all prevalent and rare complications described in PA and MMA patients, the occurrence of these complications in monogenic mitochondrial diseases and in other monogenic diseases, using data on occurrence of a phenotypic feature in genetic diseases provided by the Human Phenotype Ontology (HPO). Altogether, this review aims to provide an overview on what we, to date, do and do not understand about pathophysiology of complications occurring in PA and MMA and about the role of mitochondrial impairment herein.

2 | ENZYME DEFICIENCIES CAUSING PA AND MMA

PA and MMA are both caused by deficiencies of mitochondrial enzymes. PA is caused by a deficiency of propionyl-CoA carboxylase (encoded by *PCCA* and *PCCB*). Isolated methylmalonic acidemia (MMA) is either caused either by a deficiency of methylmalonyl-CoA mutase (MCM, encoded by *MUT*), by diminished synthesis or availability of its cofactor 5′-deoxyadenosylcobalamin which is associated with cobalamin A, B or D deficiency (encoded by *MMAA*, *MMAB* or *MMADHC*, respectively), or by a deficiency of methylmalonyl-CoA epimerase (MCE, encoded by *MCEE*). Biochemically, both PA and MMA result in accumulation of propionyl-CoA, propionic acid, 3-hydroxypropionic acid, propionylcarnitine, propionylglycine and 2-methylcitrate. Accumulation of methylmalonic acid and often methylmalonylcarnitine in MMA discriminates MMA biochemically from PA.[5] An important differential diagnosis of PA is biotin deficiency, either caused by biotinidase deficiency or holocarboxylase deficiency. Due to deficiency of biotin as cofactor for carboxylases, the activity of propionyl-CoA carboxylase is hampered, as well as the activities of 3-methylcrotonyl carboxylase, acetyl-CoA carboxylase and pyruvate carboxylase. PA can be distinguished from biotin deficiency by enzyme studies on biotinidase and holocarboxylase activities. An important differential diagnosis of isolated methylmalonic aciduria is combined methylmalonic aciduria and homocystinuria which can be caused by cobalamin C, D, F or cobalamin J deficiency. Isolated methylmalonic aciduria can be distinguished from combined methylmalonic aciduria and homocystinuria by determination of total plasma homocysteine.[5]

Within isolated MMA, the cause and range of accumulation of toxic metabolites, the natural history and the prognosis differ between the different types.[6,7] MMA caused by deficiency of MCM is often distinguished in cobalamin unresponsive patients (mut^0) and cobalamin responsive patients (mut^-). Cobalamin A deficient patients are usually cobalamin responsive, cobalamin B deficient patients can either be cobalamin unresponsive or responsive. Mut^0 and cobalamin B deficient patients are considered severely affected regarding morbidity and mortality, whereas mut^- and cobalamin A deficient patients are considered to present with a milder form of MMA. Cobalamin D deficiency can either result in combined methylmalonic aciduria and homocystinuria, in isolated homocystinuria (variant 1) or in isolated MMA (variant 2). This type of isolated MMA is very rare compared to MCM deficiency and cobalamin A and B deficiency, and results in a cobalamin responsive phenotype similar to mut^- and cobalamin A deficiency.[8] MCE deficiency is also very rare and its' natural history is very variable, with asymptomatic patients, patients presenting with acute metabolic decompensations and patients having also a sepiapterin reductase deficiency.[9] Despite the differences between the different forms of isolated MMA, many publications assemble research data on MCM, cobalamin A and cobalamin B deficiency, and discuss isolated MMA as one disease entity. Therefore, in this review we consider isolated MMA as one disease entity as well, but discuss the different types of MMA separately whenever possible.

3 | ACUTE METABOLIC DECOMPENSATIONS

PA and MMA are typically diagnosed in early childhood, usually in the neonatal period (65% for PA, 48% for MMA) and frequently after an acute metabolic decompensation.[10] To date, patients also come to clinical attention through newborn screening, enabling early initiation of treatment. However, despite this early initiation of treatment, patients are still prone to developing metabolic decompensations throughout life.[11] The predominant trigger for metabolic decompensation is catabolism, which can be induced by an increased energy demand (acute trauma, infection, fever, too much exercise or psychological stress), by reduced energy supply (fasting, vomiting), by a relatively high protein intake (inactivity) or by medication. Irrespective of the trigger, the breakdown of branched-chain amino acids acutely increases the amount of circulating toxic metabolites. The acidic nature of these metabolites rapidly causes a metabolic acidosis by decreasing the pool of bicarbonate. Oftentimes, also lactic acidosis and hyperammonemia are encountered.

Clinically, patients present with vomiting and anorexia, followed by dehydration, weight loss, lethargy, hypothermia, hypotonia, and convulsions, possibly resulting in coma, multi-organ failure and even death. Metabolic decompensations can range from very mild to very severe, and likewise, triggering events can range from minor holiday stress to severe bacterial infections. It is thought that both trigger sensitivity and severity of decompensations are mainly determined by the amount of residual activity of the affected enzyme.[12] The most important therapeutic intervention, regardless of the severity of the decompensation, is limiting protein intake and increasing the caloric intake, to stop protein catabolism. The extent to which protein intake is limited and the necessity of subsequent additional therapies is determined by the severity of the decompensation. Treatment can be immediately initiated when parents, patients and doctors recognize a decompensation and therefore, with the available therapies at hand, it is in most patients possible to prevent severe metabolic decompensations.

4 | COMPLICATIONS

Despite current care, patients with PA and MMA are prone to develop a broad range of complications, with varying prevalence, and these complications seem to occur despite apparent good metabolic control.[12] Pathophysiology of each of these complications is not well understood. Studying the prevalent complications that have been assessed in cohort studies and calculating the weighted percentage based on sample size of the cohort studies (Figure 1, Supplementary Table 1 [ST1])[13-28] revealed that in PA, hepatomegaly and/or a hyperechoic liver, cognitive deficits and anemia, psychomotor retardation and muscular hypotonia are the five most prevalent complications. In MMA, the five most prevalent complications are joint hypermobility, pes planus, cognitive deficits, enamel defects and psychomotor retardation. Despite being highly prevalent, hepatomegaly and/or a hyperechoic liver in PA and joint hypermobility, pes planus and enamel defects in MMA were each assessed in only one study (ST1) and these complications are not the most devastating ones. Complications considered important in both diseases, as indicated by the number of studies assessing these complications, are basal ganglia hyperintensities, epilepsy, pancreatitis, renal failure (in MMA) and cardiomyopathy (in PA) (ST1).

For each of the prevalent complications occurring in PA and MMA that have been assessed in cohort studies, and for each of the rare complications that have been described in case-reports (Supplementary Table 2, ST2), we summarize the current hypotheses and evidence and we assess the potential role of mitochondrial impairment for the underlying pathophysiology (Table 1).

4.1 | Brain

Many of the complications occurring in PA and MMA arise from brain damage. On magnetic resonance imaging, both white matter lesions and basal ganglia hyperintensities are found, with comparable prevalence in PA and MMA (Figure 1, ST1). These lesions, that are often permanent, can lead to a variety of clinical problems like psychomotor retardation, movement disorders (MMA > PA), cognitive deficits (PA > MMA) and psychiatric problems including attention deficit hyperactive disorder and autism (PA > MMA) (Figure 1, ST1).[29-31] Schreiber et al reviewed neurological complications in PA and state that these complications are partly induced by acute metabolic decompensations, often at initial presentation. Hyperammonemia leads to vulnerability of the astrocytes and causes cerebral edema and hypoperfusion. In addition, hypoglycemia, lactic acidosis, an increased anion gap, increased propionic acid, increased glycine and ketosis might also induce brain damage during acute metabolic decompensations.[32] It is hypothesized that due to implementation of newborn screening and early initiation of treatment, neurological damage due to the first presentation might be prevented,[11] but reports on the effect of newborn screening in PA and MMA are still scarce.[11,33-35] However, in patients with apparent good metabolic control, neurological complications can still arise over time, possibly caused by persistently increased levels of propionic acid, 2-methylcitrate, lactate and ammonia, that inhibit and deplete enzymes in the Krebs cycle (,[32] reviewed in Haijes et al,[36]). In support, increased brain lactate on magnetic resonance spectroscopy during periods of apparent good metabolic control has been demonstrated in PA children.[37] Furthermore, Frye et al[38] demonstrated an association between autism spectrum disorders and altered propionic acid metabolism affecting mitochondrial function in lymphoblastoid cell lines. For MMA the same mechanism of accumulating toxic metabolites leading to mitochondrial oxidative stress and acidosis in neurons and astrocytes ultimately leading to cellular necrosis has been proposed.[39] This claim is supported by several rat studies in which injection of anti-oxidants prevented the occurrence of neurological complications that were induced by either propionic acid or methylmalonic acid (reviewed in Haijes et al,[36]). The involvement of the basal ganglia, especially the globus pallidus, is probably due to its high energy demand, rich vascularization and elevated metabolism in that location in the first year of life.[39] The substantia nigra is histologically and functionally similar to the globus pallidus, explaining its susceptibility to the same toxic metabolites.[40]

In contrast to these permanent lesions, stroke-like episodes can also occur (Figure 1, ST1). In a stroke-like episode the process is still reversible, not leading to permanent damage.[41-44] These stroke-like episodes most often occur

somewhat later in life, but it is suggested that they might share the same pathophysiological process.[43] However, no studies or hypotheses regarding the pathophysiology of stroke-like episodes have been described.

Rare complications caused by brain damage, described in case-reports, are visual hallucinations, episodes of acute psychosis and bipolar disorder with psychotic features (Figure 1, ST2). Pathophysiology of these rare complications is not clear and may be multifactorial, for example, genetic vulnerability, the burden of a chronic disease and distressing life-events.[45] However, the toxic compounds associated to PA and MMA also appear to play a role, as therapies

TABLE 1 Evidence for the role of mitochondrial impairment in pathophysiology of complications in PA and MMA

		Literature		HPO			Conclusion
HPO code	HPO name	Hypothesis	Evidence	% mitoch.	*P*-value	Conclusion	Mitochondrial pathophysiology?
HP:0001638	Cardiomyopathy	Mitochondrial	Patient treatment	22.3	<.0001	Mitochondrial	Probably
HP:0000648	Optic atrophy	Mitochondrial	Patient treatment	17.1	<.0001	Mitochondrial	Probably
HP:0001392	Abnormality of the liver	Mitochondrial	Patient histology; Animal studies	9.7	.0339	Mitochondrial	Probably
HP:0003546	Exercise intolerance	Mitochondrial	Patient histology	51.4	<.0001	Mitochondrial	Probably
HP:0001733	Pancreatitis	Mitochondrial	Animal studies	26.8	<.0001	Mitochondrial	Probably
HP:0002134	Abnormality of the basal ganglia	Mitochondrial	Animal studies	20.0	.0306	Mitochondrial	Probably
HP:0001250	Seizures	Mitochondrial	Animal studies	11.6	<.0001	Mitochondrial	Probably
HP:0000717	Autism	Mitochondrial	Cell lines	14.3	.0284	Mitochondrial	Probably
HP:0012622	Chronic kidney disease	Mitochondrial	Patient histology; Animal studies	2.9	NS		Possibly
HP:0001903	Anemia	Mitochondrial	Patient histology	7.8	NS		Possibly
HP:0001875	Neutropenia	Mitochondrial	Patient histology	2.3	NS		Possibly
HP:0001873	Thrombocytopenia	Mitochondrial	Patient histology	3.3	NS		Possibly
HP:0001876	Pancytopenia	Mitochondrial	Patient histology	3.8	NS		Possibly
HP:0001297	Stroke	Mitochondrial	No evidence	22.2	<.0001	Mitochondrial	Possibly
HP:0000709	Psychosis	Mitochondrial	No evidence	21.8	.0001	Mitochondrial	Possibly
HP:0000407	Sensorineural hearing impairment	Inhibited potassium flow	Cell lines	12.0	.0001	Mitochondrial	Possibly
HP:0011968	Feeding difficulties	Multifactorial	No evidence	13.9	<.0001	Mitochondrial	Possibly
HP:0001252	Muscular hypotonia	NA	NA	12.7	<.0001	Mitochondrial	Possibly
HP:0001657	Prolonged QT interval	Inhibited potassium flow	Cell lines	5.9	NS		Unknown
HP:0008209	Premature ovarian insufficiency	Mitochondrial	No evidence	4.7	NS		Unknown
HP:0002019	Constipation	Multifactorial	No evidence	11.0	NS		Unknown
HP:0000682	Abnormality of dental enamel	Chronic acidosis	No evidence	1.5	NS		Unknown
HP:0001513	Obesity	NA	NA	1.4	.0084	Nonmitochondrial	Unlikely
HP:0001997	Gout	Chronic (renal) acidosis	Patient histology	0.0	NS		Unlikely
HP:0000787	Nephrolithiasis	Dehydration; Chronic acidosis; Protein restriction	Patient histology	3.4	NS		Unlikely
HP:0000964	Eczema	Isoleucine restriction	Patient treatment	1.7	NS		Unlikely

TABLE 1 (Continued)

		Literature		HPO			Conclusion
HPO code	HPO name	Hypothesis	Evidence	% mitoch.	*P*-value	Conclusion	Mitochondrial pathophysiology?
HP:0004349	Reduced bone mineral density	Protein restriction; Chronic acidosis	Patient treatment	2.5	NS		Unlikely
HP:0004322	Short stature	Protein restriction	Patient treatment	3.8	NS		Unlikely

Abbreviations: HPO, human phenotype ontology; MMA, methylmalonic acidemia; NS, not significant; PA, propionic acidemia.
% mitoch. is the percentage of the mitochondrial genes in the number of associated genes to the complication, according to HPO (see Supplementary Table 3 [ST3] for full table). *P*-value is the *P*-value resulting from a Bonferroni corrected Fisher's exact test comparing the complication to "phenotypic abnormality" (ST3). Evidence from literature is categorized in five categories: patient treatment, patient histology, animal studies, cell lines or no evidence. NA is listed when no hypothesis for the complication on pathophysiology has been described in literature. Conclusion from HPO-data is categorized in two categories: mitochondrial, if a statistical significant *P*-value is indicating overrepresentation in mitochondrial disease, or nonmitochondrial, if a statistical significant *P*-value is indicating underrepresentation in mitochondrial disease. The final conclusion whether mitochondrial impairment might play a role in the pathophysiology of the complication is categorized in five categories: "probably" if both literature and HPO data indicate a role for mitochondrial impairment, "possibly" if literature or HPO data indicate a role for mitochondrial impairment," unknown" if results are inconclusive and "unlikely" when either literature or HPO data indicate that their might be another pathophysiological process at play than mitochondrial impairment. In theory, a complication would be classified "highly unlikely" when both literature and HPO data would indicate that pathophysiology is not related to mitochondrial impairment.

inducing metabolic stability contributed to recovery of psychiatric symptoms.[46]

Another important complication induced by brain damage is epilepsy, which is more prevalent in PA than in MMA (Figure 1, ST1). There seem to be two types of epilepsy in PA and MMA. First, patients can develop epilepsy independently of acute metabolic decompensations. This type of epilepsy requires life-long anti-epileptic medication. It can be induced by structural brain lesions that arose during acute metabolic decompensations. Secondly, convulsions and even status epilepticus can arise during acute metabolic decompensations, particularly in the neonatal period. The pathophysiology of this second type of epilepsy involves two separate routes, leading to activation of the *N*-methyl-D-aspartate (NMDA) receptor and excitotoxicity. First, hyperammonemia results in inhibition of glutamate uptake and subsequent accumulation of extracellular glutamate.[47,48] This activates the NMDA-receptors[49] and leads to excessive Ca^{2+} accumulation, inducing mitochondrial depolarization in neurons and astrocytes.[47,50,51] Additionally, propionic acid, methylmalonic acid and ammonia all induce inhibition of glutamate decarboxylase. Less glutamate is converted into GABA, leading to NMDA-receptor activation and promoting excitotoxicity.[52,53] In addition to these two routes, two more processes contribute to excitotoxicity. First, glutamate dehydrogenase activity is inhibited by 2-methylcitric acid.[54] Glutamate oxidation is reduced, ATP production is reduced and the glutamine/glutamate ratio is altered, also inducing excitotoxicity.[54] Second, oxidative stress (both reactive oxygen species [ROS] and reactive nitrogen species) leads to decreased Na^+/K^+/ATPase activity,[55,56] mitochondrial depolarization and decreased ATP synthesis,[53] again promoting excitotoxicity.

4.2 | Eye

Optic atrophy is equally prevalent in PA and MMA (Figure 1, ST1). For two reasons it is hypothesized that mitochondrial impairment plays an important role.[57] First, optic atrophy occurring in MMA and PA patients resembles the clinical profile of Leber hereditary optic neuropathy and other mitochondrial optic neuropathies in terms of age at onset, presentation and progression.[57,58] Second, despite normal plasma levels, supplementation of coenzyme Q10 and α-tocopherol seems to have a beneficial effect on sight in patients suffering from optic atrophy.[59] Bilateral glaucomatous optic atrophy that resolved after anti-glaucomatous surgery has been reported in a single PA patient. The juvenile glaucoma was thought to be caused by an altered chamber angle. As this has been described only once,[60] it is doubtful whether glaucomatous optic atrophy is due to PA.

4.3 | Ear

Sensorineural hearing loss is slightly more prevalent in PA than in MMA (Figure 1, ST1). Interestingly, in one MMA patient (*MUT* type), it has been observed to occur only 3 months after the patient developed optic atrophy,[57] suggesting a shared underlying pathophysiology. Pathophysiology of sensorineural hearing loss in PA has been addressed by Grünert et al by comparing PA to Jervell and Lange-Nielsen syndrome, a syndrome that also presents with sensorineural hearing loss and prolonged QTc interval.[61] The authors propose that sensorineural hearing loss and prolonged QTc interval share a pathogenic mechanism involving potassium channels carrying the potassium current I_{KS} (encoded by *KCNQ1* or *KCNE1*). I_{KS} is essential for cardiac repolarization and important for luminal secretion of

potassium into the endolymphatic space in the inner ear. Potassium flow via this channel is inhibited by propionic acid.[61] Therefore, the authors propose that sensorineural hearing loss is the direct effect of accumulating toxic metabolites in propionic acidemia. To date, no role for mitochondrial impairment has been discussed.

4.4 | Skeletal muscle

Muscular hypotonia is more prevalent in PA than in MMA patients (Figure 1, ST1). It tends to be worse during acute metabolic decompensations, or during chronic instability. Despite its prevalence, hypotheses on pathophysiology have not been described.

Exercise intolerance, or impaired stamina, is reported in one MMA patient (*MUT* type)[62] and occurs mostly in the second decade of life. It can be very hindering in daily activities. Exercise intolerance also tends to be worse during acute metabolic decompensations, or during chronic instability. It is hypothesized that occurrence of exercise intolerance is related to inhibition of mitochondrial energy metabolism by toxic metabolites.[62] In a muscle biopsy of this MMA patient, subsarcolemmal accumulation of mitochondria was found,[62] and in a muscle biopsy of a PA patient, decreased activities of respiratory chain complex III and IV were observed,[63] supporting a role for mitochondrial energy failure in the pathogenesis of exercise intolerance.

4.5 | Heart

Cardiomyopathy, most often hypertrophic, is more frequent in PA than in MMA patients (Figure 1, ST1). Mitochondrial impairment is suggested to play a major role in pathophysiology of cardiomyopathy.[64] Baruteau et al describe a patient with severe cardiomyopathy in whom myocardial biopsy showed endocardial fibrosis and enlarged mitochondria with atypical cristae and a slightly low respiratory chain complex IV activity. Myocardial coenzyme Q10 was found to be markedly decreased. Strikingly, a high dose of coenzyme Q10 supplementation slowly led to improved cardiac function, allowing removal of mechanical cardiac support after 2 months.[64] There are no other reports addressing the possible pathophysiology of cardiomyopathy in PA and MMA.

Prolonged QTc interval (defined as >440 ms) is quite prevalent in PA, but not in MMA, although quite some variation in prevalence has been reported (Figure 1, ST1). A prolonged QTc interval indicates prolonged repolarization over the myocardium. Pathophysiology of prolonged QTc interval has been investigated in one study, by Bodi et al. They suggest that acute reduction of the repolarizing potassium currents in cardiomyocytes, induced by toxic metabolites in propionic acidemia, are responsible for the prolonged QTc interval.[65] To date, no role for mitochondrial impairment has been proposed.

4.6 | Kidneys

Renal failure is much more prevalent in MMA patients than in PA patients (Figure 1, ST1). Patients harboring a defect in *MUT* (without residual enzymatic activity, MUT^0) or *MMAB* develop more frequently renal failure (61% and 66%, respectively) than patients harboring a defect in *MUT* (with residual enzymatic activity, MUT^-) or *MMAA* (0% and 21%, respectively). In MMA patients, renal length decreases significantly over time in comparison to kidneys of healthy individuals, indicating stagnating kidney growth.[66] Histologically, extensive interstitial fibrosis, chronic inflammation and tubular atrophy are observed in patients' renal tissue. In addition, strikingly large, circular, pale mitochondria with diminished cristae are observed, with reduced cytochrome C enzyme activity and multiple OXPHOS deficiencies.[63,67,68] The decreasing glomerular filtration rate observed in MMA patients is suggested to be protective, initiated by mitochondrial dysfunction of the proximal tubule cells, to reduce the absorptive load on these cells.[67] Manoli et al[67] created a $Mut^{-/-}$ mouse model in which MCM was expressed in liver only. In the kidneys of these mice, large numbers of mitochondria with electron-dense matrices and abnormal cristae were observed in the proximal tubules. In another $Mut^{-/-}$ mouse model in which MCM was expressed in the skeletal muscle, proliferated and enlarged mitochondria were also observed in kidney tissue.[69] Altogether, it can be concluded that mitochondrial impairment plays a significant role in the pathophysiology of renal failure. This is further underlined by the observation that mice, treated with the antioxidants coenzyme Q10 and α-tocopherol showed improved glomerular filtration rate and decreased oxidative stress in renal tissue.[67]

Urolithiasis is described in a single PA patient who presented with an ammonium acid urate calculus, formed through a combination of dehydration, chronic acidotic state and the low-protein diet.[70] It has not been described in more PA patients, nor in any MMA patient (Figure 1, ST1), but it might not have been recognized as a complication of the disease.

4.7 | Pancreas

Pancreatitis is equally prevalent in PA as in MMA patients (Figure 1, ST1). Pathophysiology of pancreatitis in PA and MMA is scarcely addressed in literature. Kahler et al[71] suggested two potential mechanisms: either activation of pancreatic enzymes in inappropriate locations, or inability of the pancreas to withstand normal metabolic stress. The

inability to withstand metabolic stress might be caused by free radical formation and deficiencies of carnitine, methionine and antioxidants. This latter theory was supported by Chandler et al, who found megamitochondria in pancreatic tissue of *Mut*$^{-/-}$ mice. In contrast to hepatocytes, megamitochondria in pancreatic tissue developed only later in life.[72] It is not reported whether these mice had suffered from pancreatitis. Megamitochondria formation is an adaptive process to unfavorable environments and is often induced by free radicals, as illustrated by the observation that formation of megamitochondria is successfully suppressed by anti-oxidants.[73] If intracellular ROS can be decreased, mitochondria can normalize both structurally and functionally, but if concentrations of free radicals become too high, apoptosis is induced.[73] Thus, the presence of megamitochondria in pancreatic tissue of *Mut*$^{-/-}$ mice might suggest a role for mitochondrial failure in pathophysiology of pancreatitis.

4.8 | Liver

Hepatomegaly and/or hyperechoic liver are reported in PA patients more often than in MMA patients (Figure 1, ST1). In addition, Kölker et al describe that the mean concentration of alanine aminotransferase is 12% above the reference range in MMA and 16% in PA patients. For aspartate aminotransferase this is 20% in MMA and 19% in PA patients and for gamma-glutamyl transferase the reported value is 9% and 33% in MMA and 10% and 25% in PA patients.[74,75] Fibrosis/cirrhosis diagnosed by liver biopsy is described in three patients, with decreased respiratory chain activities.[74] Chandler et al[72] described megamitochondria with dysmorphic and shortened cristae, and a less electron-dense mitochondrial matrix in hepatocytes of *Mut*$^{-/-}$ mice with MMA, already early in life. They found similar morphological changes in the hepatocytes of a MMA patient (*MUT* type). In line with this, in a *Mut* $^{-/-}$ mouse model in which MCM was expressed in the skeletal muscle, megamitochondria with shortened or no cristae were observed in hepatocytes. These findings were accompanied by decreased activity of the respiratory chain complex and reduced oxidation rates of substrates that depend on mitochondrial function for their metabolism.[69] These findings suggest a prominent role for mitochondrial failure in pathophysiology of liver involvement in PA and MMA.

Two MMA patients (both *MUT* type) presented with a hepatoblastoma (Figure 1, ST1). The first was a patient who received growth hormone therapy for 10 months and immunosuppressive therapy after a kidney transplant at 9.7 years. The patient developed a hepatoblastoma at the age of 11 years and died during the first weeks of chemotherapy.[76,77] The second patient also developed a hepatoblastoma, but is in remission since he received an orthotopic split-liver-kidney transplant.[78] In this report it was speculated that increased levels of ROS led to DNA damage, affecting oncogenes or tumor-suppressor genes, although no supporting evidence was presented.[78]

4.9 | Gastro-intestinal system

Touati et al describe 55% of PA and MMA patients having intermediate or major feeding disorders at 3 years of age, improving with age (35% at 6 years, 12% at 11 years). A total of 60% of patients were tube-fed overnight or continuously, decreasing with age (48% at 6 years, 27% at 11 years), although a significant part of the patients remains dependent on tube-feeding throughout life.[79,80] Pathophysiology of feeding problems is hard to assess and likely multi-factorial, with an important role for the strict protein-restricted diet, the constant focus on feeding and the need for continuous tube-feeding in the first years of life to prevent catabolism.

Constipation is described as an important problem in PA and MMA patients,[12,81] but its prevalence has been described in only one study among PA patients (Figure 1, ST1). Constipation is known to contribute to metabolic instability and requires treatment upon occurrence.[12,81] However, the reason for its (presumed) increased prevalence and the pathophysiology in PA and MMA is not addressed in literature. Accumulating toxic metabolites might play a role through affected bowel innervation and mitochondrial energy deficiency, resulting in decreased peristalsis, but a relative lack of fibers and fluids, a relative lack of physical exercise, impaired cognition and psychosocial stress might also contribute to constipation.

4.10 | Ovaries

Premature ovarian failure is described in two PA patients (Figure 1, ST1). Lam et al[82] suggest that since premature ovarian failure is associated with mitochondrial diseases, with oxidative stress playing an important role, mitochondrial failure might also cause premature ovarian failure in PA, but this has not been studied yet.

4.11 | Bone marrow

Anemia, neutropenia, thrombocytopenia and pancytopenia are quite frequent in PA patients, but in MMA cohort studies, the prevalence of these complications has not been assessed (Figure 1, ST1). Kölker et al describe that the mean level of hemoglobin is 40% below the reference range in MMA patients and 22% in PA patients. Leukocytes are on average 7% below the reference range in MMA patients and 18% in PA patients. Thrombocytes are on average 6% below the

reference range in MMA patients and 18% in PA patients.[75] Severe decreases of hemoglobin, leukocytes and thrombocytes can occur during acute metabolic decompensations, and milder decreases occur also in a more chronic fashion.[83]

Rare complications, described in case-reports, are hemophagocytotic lymphohistiocytosis and myelodysplastic syndrome (Figure 1, ST2). Proliferation and maturation of bone marrow stem cells is affected by propionic acid and methylmalonic acid.[83-85] Also, accumulation of intracellular propionic acid and/or methylmalonic acid or changes in membrane lipid composition may lead to erythrophagocytosis, hence shortened survival of erythrocytes. A role for mitochondrial dysfunction, leading to compromised aerobic respiration and inflammasome activation by oxidative stress is proposed as well.[86] Ineffective erythropoiesis caused by mitochondrial dysfunction is further supported by the observation of mitochondrial iron accumulation represented by ring sideroblasts in myelodysplastic syndrome in an MMA patient (*MUT* type).[87] Hypogammaglobulinemia, described in four PA patients (Figure 1, ST2) might be caused concordantly, by affected proliferation and maturation of bone marrow cells due to a combination of energetic failure and oxidative stress, but there is no evidence to support this hypothesis.

4.12 | Bone

Decreased bone mineral density (BMD) is widely accepted to be a complication of the life-long protein restricted diet in combination with the accumulating acids, rather than being the direct, specific effect of toxic metabolites accumulating in PA and MMA. Decreased BMD has been described in PA patients but has not systematically been assessed in MMA patients (Figure 1, ST1). A severely decreased BMD can result in pathological fractures.[88,89] Medical food containing the allowed amino acids cannot fully prevent decreased BMD. Instead, it is suggested that amino acid mixtures might even contribute to decreased BMD, since they increase the—already high—acid load for the kidneys, inducing buffering of H^+ ions in the bone. This evokes increased bone resorption and lowers BMD. In addition, due to subtle deficiencies of amino acids such as proline and lysine, biosynthesis of collagen might be impaired, reducing the tensile strength of the bone matrix.[90] Instead of amino acid mixtures, it is proposed that intact protein supplementation, lacking the amino acids isoleucine, valine, methionine and threonine, might be more effective in preventing decreased BMD.[90]

4.13 | Joints

Joint hypermobility and pes planus are both described in only one cohort study of MMA patients,[79] but the prevalence (69% joint hypermobility and 60% pes planus) suggests that both complications are more prevalent than previously acknowledged (Figure 1, ST1), although severe patients might be over-represented in this cohort.[79]

Juvenile gout has been described in two MMA patients (both *MMAB* type) (Figure 1, ST1). Both patients presented with chronic kidney disease due to renal tubular acidosis. In the proximal tubule, the acidosis may compete with the uric acid excretion, causing long-lasting hyperuricemia in plasma and the formation of monosodium-urate crystals.[91] This has not been described in any PA patient, nor in any MMA patient without chronic kidney disease.

4.14 | Growth

Growth retardation, resulting in a short stature is more frequent in MMA patients than in PA patients (Figure 1, ST1). Growth retardation is most likely secondary to the protein restricted diet rather than a direct effect of PA and MMA.[92] In *Mut* $^{-/-}$ mice in which MCM was expressed in the skeletal muscle, and which were on a diet resembling the diet used for the management of MMA patients, growth failure was observed throughout their life span.[69] Proteins, especially in early life, are essential for normal growth and a relative lack of protein results in impaired growth.

Feillet et al[93] reported a resting energy expenditure (REE) of 80% compared to the prediction of the Schofield height and weight equation, in both PA and MMA patients. They speculate that mitochondrial impairment could contribute to the decreased REE, but they do not present any evidence. The finding of a decreased REE in PA and MMA was supported by Thomas et al,[94] but van Hagen et al[95] did not find a decreased REE in PA and MMA patients. They suggested that adequate caloric intake, and possibly the intake of synthetic amino acid mixtures might result in a normal REE. To test this hypothesis, Hauser et al[96] normalized measured REE to fat free mass for MMA patients and found that normalized REE is decreased in MMA patients and that it is influenced by both creatinine clearance and body length.

The prevalence of obesity, which is mainly in the adult population an important complication of the diet used to treat PA and MMA, has not been systematically assessed (Figure 1, ST1). Hauser et al[96] report that fat free mass is decreased, and BMI is increased in some MMA patients. It is expected that the prevention of catabolism through a hypercaloric diet, often with continuous overnight feeding, takes place at the expense of weight gain. Attempts to lose extra weight go along with the risk of protein catabolism. Although it differs from patient to patient, the balance between overweight and acute metabolic decompensations can be very tight.

4.15 | Skin

Skin problems, often described as acrodermatitis dysmetabolica, are described in both PA and MMA patients (Figure 1, ST1) and also in patients with other organic acidemias. It is presumed to be the result of an isolated isoleucine deficiency since symptoms can resolve quickly upon isoleucine supplementation,[97-100] but it has also be considered the result of a more complex multi-deficiency syndrome.[101] In one patient with MMA, erythema nodosum is described, which resolved in a few days upon high dose vitamin B12 treatment[102] and in one patient with PA, necrolytic migratory erythema is described, which is considered to be the result of zinc deficiency in this patient.[103]

4.16 | Teeth

Bassim et al describe that enamel defects occur significantly more often in the MMA patients included in their study than in the matched control patients (Figure 1, ST1). The higher the methylmalonic acid, the more enamel defects, especially in patients harboring the *MUT* type. Pathophysiology is unknown, but it is hypothesized that enamel defects are caused by severe pediatric disease, by renal insufficiency, or by local influence of methylmalonic acid on tooth genesis.[104] Enamel defects have not been assessed in PA patients.

5 | OCCURRENCE OF COMPLICATIONS IN PA AND MMA IN OTHER MONOGENIC MITOCHONDRIAL DISEASES

For many complications, it is hypothesized that mitochondrial impairment contributes to their pathophysiology (Table 1). Next to what is reported in literature, we here add an extra line of evidence using data on occurrence of a phenotypic feature in genetic diseases, provided by HPO. We assume that complications resulting from mitochondrial impairment are overrepresented in monogenetic mitochondrial diseases and conversely, that complications not caused by mitochondrial impairment are underrepresented in mitochondrial disease. Based on this assumption, we studied the occurrence of the complications in PA and MMA in both monogenic mitochondrial diseases and in other monogenic diseases. We used data provided by HPO and an extensive review on monogenic mitochondrial disorders, listing all genes associated with mitochondrial disease, both nuclear and mitochondrial.[105] For each complication we identified the number of genes associated with this complication according to HPO. Of these genes, we determined the number of genes causing monogenic mitochondrial disease (both nuclear and mitochondrial genes).[105] Next, we calculated the percentage of mitochondrial genes within the group of genes associated with the complication (Supplementary Table 3, ST3). Using the phenotypic feature "phenotypic abnormality" (HP:0000118) as a reference, a Fisher's exact test was performed to compare for each complication the percentage of mitochondrial genes to this reference (6.3% mitochondrial genes, ST3). *P*-values were corrected for multiple testing according to the Bonferroni method. Figure 2 demonstrates the underrepresentation and overrepresentation of the different complications occurring in PA and MMA in mitochondrial disease and the conclusions retrieved from these calculations are presented in Table 1.

Underlining the mitochondrial nature of these complications, the complications exercise intolerance, pancreatitis, cardiomyopathy, stroke, psychosis, abnormality of the basal ganglia, optic atrophy, autism, feeding problems, muscular hypotonia, sensorineural hearing impairment, seizures and abnormality of the liver are symptoms that are significantly overrepresented in monogenic mitochondrial diseases (Table 1 and Figure 2), suggesting that indeed mitochondrial impairment plays a role in pathophysiology of these complications. For anemia the percentage of mitochondrial diseases was increased compared to "phenotypic abnormality," but not significantly. Contrary, the complication obesity is significantly underrepresented in monogenic mitochondrial diseases, suggesting that indeed its' pathophysiology is not associated with mitochondrial impairment (Table 1 and Figure 2). For gout, abnormality of dental enamel, acrodermatitis dysmetabolica, reduced bone mineral density, nephrolithiasis and short stature, the percentage of mitochondrial diseases was decreased compared to "phenotypic abnormality," but not significantly.

Not all complications are as overrepresented among monogenic mitochondrial diseases as expected: chronic kidney disease, anemia, neutropenia, thrombocytopenia, pancytopenia and premature ovarian insufficiency are not more frequent in mitochondrial disease, while a mitochondrial role in pathophysiology is expected (Table 1).

It should be noted that the validity of this extra line of evidence supporting the hypothesis that pathophysiology of many complications in PA and MMA is related to mitochondrial failure is limited. This approach relies on the accuracy and completeness of HPO and has not been validated for other (mitochondrial) diseases yet. Still, the results of this extra line of evidence are reasonably similar to what has been reported in literature (Table 1).

6 | THE ROLE OF MITOCHONDRIAL IMPAIRMENT IN PATHOPHYSIOLOGY OF COMPLICATIONS IN PA AND MMA

Based on reports of patients treated with anti-oxidants, histology of patient tissue, animal studies and studies in cell lines, combined with supporting evidence from the occurrence of complications in other monogenic mitochondrial

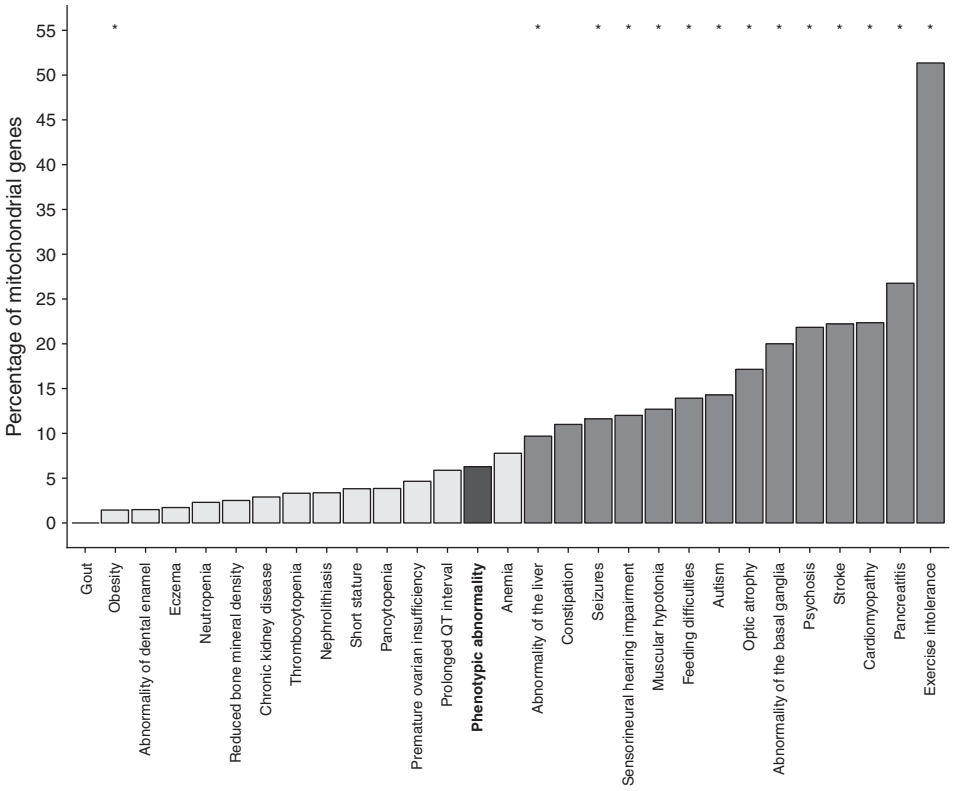

FIGURE 2 Association to mitochondrial disease for complications occurring in PA and MMA. Complications significantly overrepresented in mitochondrial disease are depicted in red. Complications not significantly overrepresented in mitochondrial disease are depicted in light gray. **P*-value <.05 determined by a Fisher's exact test with multiple testing correction according to the Bonferroni method, comparing the percentage of the complication to the reference phenotype "phenotypic abnormality," which is depicted in dark gray

diseases, we conclude that mitochondrial impairment probably plays a role in pathophysiology of cardiomyopathy, optic atrophy, abnormality of the liver, exercise intolerance, pancreatitis, abnormality of the basal ganglia, seizures and autism (Table 1). Contrary, we consider a role for mitochondrial impairment unlikely for short stature, reduced BMD, acrodermatitis dysmetabolica, nephrolithiasis, gout and obesity (Table 1).

Interestingly, to date there is no evidence suggesting that mitochondrial impairment plays a role in the pathophysiology of prolonged QTc interval, nor is it overrepresented in monogenic mitochondrial diseases (Table 1). In contrast, sensorineural hearing loss is overrepresented in mitochondrial disease (Table 1), although a shared pathophysiological process involving inhibited potassium flow due to propionic acid is suspected.[61] This might implicate that in hearing loss in mitochondrial disease another pathophysiological process might be at play, that both complications do not share the same pathophysiology, or that prolonged QTc is underreported or underdiagnosed in monogenic mitochondrial diseases.

7 | KNOWING THE UNKNOWNS

Mitochondrial failure is likely to play a major role in pathophysiology of many devastating PA and MMA complications. However, despite this knowledge, we still cannot predict for any given patient when these complications will occur, which tissue will be affected and whether that effect will be reversible or permanent, while this is crucial knowledge for determining the therapeutic window of opportunity and the target tissue(s). Questions that need answers in the (near) future include: What is the nature of the differences in age of onset, why do patients develop complications during periods with (seemingly) good metabolic control and what determines reversibility of the different mitochondrial complications? Is this solely determined by residual enzymatic activity or does the strictness of and compliance to the protein restriction and other therapies play a role? What is the influence of the number, severity and duration of metabolic decompensations? Next to these questions addressing interpatient differences, what determines in one patient the intertissue differences in susceptibility for complications if there are no differences in enzymatic activity, therapy compliance or metabolic decompensations? Answers to these questions might be the key towards therapy improvements including the determination of the therapeutic window of opportunity and the target tissue(s).

8 | CONCLUSION

Current treatment strategies are inadequate to prevent or treat most complications in PA and MMA. To optimize treatment strategies, insight in the pathophysiology of complications in PA and MMA is crucial. Here we summarized the current hypotheses and evidence on underlying pathophysiology of

these complications, we assessed the occurrence of these complications in (other) monogenic mitochondrial diseases and we report whether mitochondrial impairment might play a role in the pathophysiology of the complication (Table 1). Altogether, this is a comprehensive overview on what we, to date, do and do not understand about pathophysiology of complications occurring in PA and MMA and about the role of mitochondrial impairment herein.

9 | WEB RESOURCES

Human Phenotype Ontology, http://compbio.charite.de/hpoweb/

ACKNOWLEDGMENTS

This work was supported by the personal Alexandre Suerman Stipend of the University Medical Centre Utrecht (H.A.H.). N.M.V.-D. declares that she will accept full responsibility for the work and the conduct of the study. She had access to the data and controlled the decision to publish.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

H.A.H., P.M.H., J.J.M.J., and N.M.V.-D. conceived the research. P.M.H., J.J.M.J., and N.M.V.-D. supervised the research. H.A.H. and S.Y.T. performed the systematic data-analysis. H.A.H. performed the analysis of Human Phenotype Ontology data and wrote the manuscript. All authors edited and reviewed the manuscript and approved the final version.

ETHICS STATEMENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

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REFERENCES

1. Childs B, Nyhan WL, Borden M, Bard L, Cooke RE. Idiopathic hyperglycinemia and hyperglycinuria: a new disorder of amino acid metabolism I. *Pediatrics*. 1961;27:522-538.
2. Nyhan WL, Borden M, Childs B. Idiopathic hyperglycinemia: a new disorder of amino acid metabolism. II. The concentrations of other amino acids in the plasma and their modification by the administration of leucine. *Pediatrics*. 1961;27:539-550.
3. Matsui SM, Mahoney MJ, Rosenberg LE. The natural history of the inherited methylmalonic acidemias. *N Engl J Med*. 1983;308:857-861.
4. Roe CR, Millington DS, Maltby DA, Bohan TP, Hoppel CL. L-Carnitine enhances excretion of propionyl coenzyme a as propionylcarnitine in propionic acidemia. *J Clin Invest*. 1984;73:1785-1788.
5. Fowler B, Leonard JV, Baumgartner MR. Causes of and diagnostic approach to methylmalonic acidurias. *J Inherit Metab Dis*. 2008;31:350-360.
6. Hörster F, Baumgartner MR, Viardot C, et al. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut^0, mut^-, clbA, clbB). *Pediatr Res*. 2007;62:225-230.
7. Manoli I, Sloan JL, Venditti CP. Isolated methylmalonic acidemia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle, WA: University of Washington, Seattle; 2016.
8. Parini R, Furlan F, Brambilla A, et al. Severe neonatal metabolic decompensation in methylmalonic academia caused by CblD defect. *JIMD Rep*. 2013;11:133-137.
9. Abily-Donval L, Torre S, Samson A, et al. Methylmalonyl-CoA epimerase deficiency mimicking propionic aciduria. *Int J Mol Sci*. 2017;18(11):2294.
10. Kölker S, Garcia Cazorla A, Valayannopoulos V, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation. *J Inherit Metab Dis*. 2015a;38:1041-1057.
11. Grünert SC, Müllerleile S, de Silva L, et al. Propionic acidemia: neonatal versus selective metabolic screening. *J Inherit Metab Dis*. 2012;35:41-49.
12. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis*. 2014;9:130.
13. AlGhamdi A, Alrifai MT, Al Hammad AI, et al. Epilepsy in propionic acidemia: case series of 14 Saudi patients. *J Child Neurol*. 2018;33(11):713-717.
14. Baumgarter ER, Viardot C. Long-term follow-up of 77 patients with isolated methylmalonic acidaemia. *J Inherit Metab Dis*. 1995;18(2):138-142.
15. Baumgartner D, Scholl-Burgi S, Sass JO, et al. Prolonged QTc intervals and decreased left ventricular contractility in patients with propionic acidemia. *J Pediatr*. 2007;150:192-197.
16. Brismar J, Ozand PT. CT and MR of the brain in disorders of the propionate and methylmalonate metabolism. *AJNR Am J Neuroradiol*. 1994;15(8):1459-1473.
17. Cosson MA, Benoist JF, Touati G, et al. Long-term outcome in methylmalonic aciduria: a series of 30 French patients. *Mol Genet Metab*. 2009;97:172-178.
18. Gokce M, Unal O, Hismi B, et al. Secondary hemophagocytosis in 3 patients with organic acidemia involving propionate metabolism. *Pediatr Hematol Oncol*. 2012;29:92-98.
19. Griffin TA, Hostoffer RW, Tserng KY. Parathyroid hormone resistance and B cell lymphopenia in propionic acidemia. *Acta Paediatr*. 1996;85:875-878.

20. Grotto S, Sudrié-Arnaud B, Drouin-Garraud V. Dilated cardiomyopathy and premature ovarian failure unveiling propionic aciduria. *Clin Chem*. 2018;64:752-754.
21. Grünert SC, Müllerleile S, de Silva L, et al. Propionic acidemia: clinical course and outcome in 55 pediatric and adolescent patients. *Orphanet J Rare Dis*. 2013;8:6.
22. Haberlandt E, Canestrini C, Brunner-Krainz M, et al. Epilepsy in patients with propionic acidemia. *Neuropediatrics*. 2009;40:120-125.
23. Hörster F, Garbade SF, Zwickler T, et al. Prediction of outcome in isolated methylmalonic acidurias: combined use of clinical and biochemical parameters. *J Inherit Metab Dis*. 2009;32:630-639.
24. Karimzadeh P, Jafari N, Ahmad Abadi F, et al. Methylmalonic acidemia: diagnosis and neuroimaging findings of this neurometabolic disorder (an Iranian pediatric case series). *Iran J Child Neurol*. 2013;7(3):63-66.
25. Karimzadeh P, Jafari N, Ahmad Abadi F, et al. Propionic acidemia: diagnosis and neuroimaging findings of this neurometabolic disorder. *Iran J Child Neurol*. 2014;8(1):58-61.
26. Kasapkara CS, Kangin M, Ozmen BO, et al. Seconday hemophagocytosis in propionic acidemia. *Iran J Pediatr*. 2015; 25:e339.
27. Ma X, Zhang Y, Yang Y, et al. Epilepsy in children with methylmalonic acidemia: electroclinical features and prognosis. *Brain Dev*. 2011;33:790-795.
28. MacFarland S, Hartung H. Panctyopenia in a patient with methylmalonic acidemia. *Blood*. 2015;125:1840.
29. Al-Owain M, Kaya N, Al-Shamrani H, et al. Autism spectrum disorder in a child with propionic acidemia. *JIMD Rep*. 2013;7: 63-66.
30. Dejean de la Batie C, Barbier V, Roda C, et al. Autism spectrum disorders in propionic acidemia patients. *J Inherit Metab Dis*. 2018;41:623-629.
31. Witters P, Debbold E, Crivelly K, et al. Autism in patients with propionic acidemia. *Mol Genet Metab*. 2016;119:317-321.
32. Schreiber J, Chapman KA, Summar ML. Neurologic considerations in propionic acidemia. *Mol Genet Metab*. 2012;105:10-15.
33. Couce ML, Castiñeiras DE, Bóveda MD, et al. Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded newborn screening programme. *Mol Genet Metab*. 2011;104(4):470-475.
34. Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis*. 2006;29(2–3):383-389.
35. Heringer J, Valayannopoulos V, Lund AM, et al. Impact of age at onset and newborn screening on outcome in organic acidurias. *J Inherit Metab Dis*. 2016;39(3):341-353.
36. Haijes HA, van Hasselt PM, Jans JJM, Verhoeven-Duif NM. Pathophysiology of propionic and methylmalonic acidemias. Part 2: Complications. *J Inherit Metab Dis*. 2019. https://doi.org/10.1002/jimd.12128.
37. Chemelli AP, Schocke M, Sperl W, Trieb T, Aichner F, Felber S. Magnetic resonance spectroscopy (MRS) in five patients with treated propionic acidemia. *J Magn Reson Imaging*. 2000;11: 596-600.
38. Frye RE, Rose S, Chacko J, et al. Modulation of mitochondrial function by the microbiome metabolite propionic acid in autism and control cell lines. *Transl Psychiatry*. 2016;6:e927.
39. Andreula CM, De Blasi R, Carella A. CT and MR studies of methylmalonic acidemia. *AJNR Am J Neuroradiol*. 1991;12: 410-412.
40. Baker EH, Sloan JL, Hauser NS, et al. MRI characteristics of globus pallidus infarcts in isolated methylmalonic acidemia. *AJNR Am J Neuroradiol*. 2015;36:194-201.
41. Chakrapani A, Sivakumar P, McKiernan PJ, Leonard JV. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. *J Pediatr*. 2002;140:261-263.
42. Heidenreich R, Natowicz M, Hainline BE, et al. Acute extrapyramidal syndrome in methylmalonic acidemia: "metabolic stroke" involving the globus pallidus. *J Pediatr*. 1988;113(6):1022-1027.
43. Karall D, Haberlandt E, Schimmel M, et al. Cytotoxic not vasogenic edema is the cause for stroke-like episodes in propionic acidemia. *Neuropediatrics*. 2011;42:210.
44. Scholl-Burgi S, Haberlandt E, Gotwald T, et al. Stroke-like episodes in propionic acidemia caused by central focal metabolic decompensation. *Neuropediatrics*. 2009;40(2):76-81.
45. Dejean de la Batie C, Barbier V, Valayannopoulos V, et al. Acute psychosis in propionic acidemia: 2 case reports. *J Child Neurol*. 2014;29:274-279.
46. Sheikhmoonesi F, Shafaat A, Moarefian S, Zaman T. Affective disorder as the first manifestation of methylmalonic acidemia: a case report. *Iran J Pediatr*. 2013;23:245-246.
47. Felipo V, Kosenko E, Miñana MD, Marcaida G, Grisolía S. Molecular mechanism of acute ammonia toxicity and of its prevention by L-carnitine. *Adv Exp Med Biol*. 1994;368:65-77.
48. Zhou BG, Noremberg MD. Ammonia downregulates GLAST mRNA glutamate transporter in rat astrocyte cultures. *Neurosci Lett*. 1999;276:145-148.
49. Lai JC, Cooper AJ. Neurotoxicity of ammonia and fatty acids: differential inhibition of mitochondrial dehydrogenases by ammonia and fatty acyl coenzyme a derivatives. *Neurochem Res*. 1991;16:795-803.
50. Schinder AF, Olson EC, Spitzer NC, Montal M. Mitochondrial dysfunction is a primary event in glutamate neurotoxicity. *J Neurosci*. 1996;16:6125-6133.
51. White RJ, Reynolds IJ. Mitochondrial depolarization in glutamate-stimulated neurons: an early signal specific to excitotoxin exposure. *J Neurosci*. 1996;16:5688-5697.
52. Malfatti CRM, Perry MLS, Schweigert ID, et al. Convulsions induced by methylmalonic acid are associated with glutamic acid decarboxylase inhibition in rats: a role for GABA in the seizures presented by methylmalonic acidemia patients? *Neuroscience*. 2007;146:1879-1887.
53. Royes LFF, Gabbi P, Ribeiro LR, et al. A neuronal disruption in redox homeostasis elicited by ammonia alters the glycine/glutamate (GABA) cycle and contributes to MMA-induced excitability. *Amino Acids*. 2016;48:1373-1389.
54. Amaral AU, Cecatto C, Castilho RF, Wajner M. 2-Methylcitric acid impairs glutamate metabolism and induces permeability transition in brain mitochondria. *J Neurochem*. 2016;137:62-75.
55. Malfatti CRM, Royes LF, Francescato L, et al. Intrastriatal methylmalonic acid administration induces convulsions and TBARS production, and alters Na^+,K^+-ATPase activity in the rat striatum and cerebral cortex. *Epilepsia*. 2003;44:761-767.
56. Wyse AT, Streck EL, Barros SV, Brusque AM, Zugno AI, Wajner M. Methylmalonate administration decreases Na^+, K^+-

ATPase activity in cerebral cortex of rats. *Neuroreport*. 2000;11: 2331-2334.
57. Traber G, Baumgartner MR, Schwarz U, Pangalu A, Donath MY, Landau K. Subacute bilateral visual loss in methylmalonic acidemia. *J Neuroophthalmol*. 2011;31:344-346.
58. Sadun AA. Mitochondrial optic neuropathies. *J Neurol Neurosurg Psychiatry*. 2002;72:424-426.
59. Pinar-Sueiro S, Martínez-Fernández R, Lage-Medina S, Aldamiz-Ecchevarria L, Vecino L. Optic neuropathy in methylmalonic acidemia: the role of neuroprotection. *J Inherit Metab Dis*. 2010; 33:199-203.
60. Rosentreter A, Gaki S, Dinslage S, Dietlein TS. Juvenile glaucoma in propionic acidemia. *Ophthalmologe*. 2012;109:1211-1213.
61. Grünert SC, Bodi L, Odening KE. Possible mechanisms for sensorineural hearing loss and deafness in patients with propionic acidemia. *Orphanet J Rare Dis*. 2017;12:30.
62. Østergaard E, Wibrand F, Ørngreen MC, Vissing J, Horn N. Impaired energy metabolism and abnormal muscle histology in mut-methylmalonic aciduria. *Neurology*. 2005;65(6):931-933.
63. de Keyzer Y, Valayannopoulos V, Benoist JF, et al. Multiple OXPHOS deficiency in the liver, kidney, heart and skeletal muscle of patients with methylmalonic aciduria and propionic aciduria. *Pediatr Res*. 2009;66(1):91-95.
64. Baruteau J, Hargreaves I, Krywawych S, et al. Successful reversal of propionic acidaemia associated cardiomyopathy: evidence for low myocardial coenzyme Q10 status and secondary mitochondrial dysfunction as an underlying pathophysiological mechanism. *Mitochondrion*. 2014;17:150-156.
65. Bodi I, Grünert SC, Becker N, et al. Mechanisms of acquired long QT syndrome in patients with propionic acidemia. *Heart Rhythm*. 2016;13:1335-1345.
66. Kruszka PS, Manoli I, Sloan JL, Kopp JB, Venditti CP. Renal growth in isolated methylmalonic acidemia. *Genet Med*. 2013;15: 990-996.
67. Manoli I, Sysol JR, Li L. Targeting proximal tubule mitochondrial dysfunction attenuates the renal disease of methylmalonic acidemia. *Proc Natl Acad Sci U S A*. 2013;110:13552-13557.
68. Zsengellér ZK, Aljinovic N, Teot LA, et al. Methylmalonic acidemia: a megamitochondrial disorder affecting the kidney. *Pediatr Nephrol*. 2014;29:2139-2146.
69. Manoli I, Sysol JR, Epping MW. FGF21 underlies a hormetic response to metabolic stress in methylmalonic acidemia. *JCI Insight*. 2018;3(23):e124351.
70. Yilmaz AC, Kiliç M, Büyükkaragüz B, Tayfur AC, Koçak M. Urolithiasis in an infant with propionic acidemia: answer. *Pediatr Nephrol*. 2015;30:77-78.
71. Kahler SG, Sherwood WG, Woolf D, et al. Pancreatitis in patients with organic acidemias. *J Pediatr*. 1994;124(2):239-243.
72. Chandler RJ, Zerfas PM, Shanske S, et al. Mitochondrial dysfunction in *mut* methylmalonic acidemia. *FASEB J*. 2009;23: 1252-1261.
73. Wakabayashi T. Megamitochondria formation – physiology and pathology. *J Cell Mol Med*. 2002;6:497-538.
74. Imbard A, Garcia Segarra N, Tardieu M, et al. Long-term liver disease in methylmalonic and propionic acidemias. *Mol Genet Metab*. 2018;123:433-440.
75. Kölker S, Valayannopoulos V, Burlina AB, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. *J Inherit Metab Dis*. 2015b;38: 1059-1074.
76. Brassier A, Boyer O, Valayannopoulos V, et al. Renal transplantation in 4 patients with methylmalonic aciduria: a cell therapy for metabolic disease. *Mol Genet Metab*. 2013;110:106-110.
77. Cosson MA, Touati G, Lacaille F, et al. Liver hepatoblastoma and multiple OXPHOS deficiency in the follow-up of a patient with methylmalonic aciduria. *Mol Genet Metab*. 2008;95:107-109.
78. Chan R, Mascarenhas L, Boles RG, Kerkar N, Genyk Y, Venkatramani R. Hepatoblastoma in a patient with methylmalonic aciduria. *Am J Med Genet A*. 2014;167:635-638.
79. Ktena YP, Paul SM, Hauser NS, et al. Delineating the spectrum of impairments, disabilities and rehabilitation needs in methylmalonic acidemia (MMA). *Am J Med Genet*. 2015;167A(9): 2075-2084.
80. Touati G, Valayannopoulos V, Mention K, et al. Methylmalonic and propionic acidurias: management without or with a few supplements of specific amino acid mixture. *J Inherit Metab Dis*. 2006;29:288-298.
81. Prasad C, Nurko S, Borovoy J, Korson MS. The importance of gut motility in the metabolic control of propionic acidemia. *J Pediatr*. 2004;144:532-535.
82. Lam C, Desviat LR, Perez-Cerda C, Ugarte M, Barshop BA, Cederbaum S. 45-year-old female with propionic acidemia, renal failure, and premature ovarian failure; late complications of propionic acidemia? *Mol Genet Metab*. 2011;103:338-340.
83. Stork LC, Ambruso DR, Wallner SF, et al. Pancytopenia in propionic acidemia: hematologic evaluation and studies of hematopoiesis in vitro. *Pediatr Res*. 1986;20:783-788.
84. Corazza F, Blum D, Clercx A, Mardens Y, Fondu P. Erythroblastopenia associated with methylmalonic aciduria. *Case Rep in vitro Stud Biol Neonate*. 1996;70(5):304-310.
85. Inoue S, Krieger I, Sarnaik A, Ravindranath Y, Fracassa M, Ottenbreit MJ. Inhibition of bone marrow stem cell growth in vitro by methylmalonic acid: a mechanism for pancytopenia in a patient with methylmalonic acidemia. *Pediatr Res*. 1981;15: 95-98.
86. Sulaiman RA, Shaheen MY, Al-Zaidan H, et al. Hemophagocytic lymphohistiocytosis: a rare cause of recurrent encephalopathy. *Intract Rare Dis Res*. 2016;5:227-230.
87. Bakshi NA, Al-Anzi T, Mohamed S, et al. Spectrum of bone marrow pathology and hematological abnormalities in methylmalonic acidemia. *Am J Med Genet A*. 2018;176:687-691.
88. Inoue F, Terada N, Nukina S, Kodo N, Kinugasa A, Sawada T. Methylmalonic aciduria with pathological fracture. *J Inherit Metab Dis*. 1993;16(6):1052-1053.
89. Talbot JC, Gummerson NW, Kluge W, Shaw DL, Groves C, Lealman GT. Osteoporotic femoral fracture in a child with propionic acidaemia presenting as non-accidental injury. *Eur J Pediatr*. 2006;165(7):496-497.
90. Ney DM, Etzel MR. Designing medical foods for inherited metabolic disorders: why intact protein is superior to amino acids. *Curr Opin Biotechnol*. 2017;44:39-45.
91. Charuvanij S, Pattaragarn A, Wisuthsarewong W, Vatanavicharn N. Juvenile gout in methylmalonic acidemia. *Pediatr Int*. 2016;58:501-503.
92. Yannicelli S. Nutrition therapy of organic acidaemias with amino acid-based formulas: emphasis on methylmalonic and propionic acidaemia. *J Inherit Metab Dis*. 2006;29(2–3):281-287.

93. Feillet F, Bodamer OA, Dixon MA, Sequeira S, Leonard JV. Resting energy expenditure in disorders of propionate metabolism. *J Pediatr*. 2000;136(5):659-663.
94. Thomas JA, Bernstein LE, Greene CL, Koeller DM. Apparent decreased energy requirements in children with organic acidemias: preliminary observations. *J Am Diet Assoc*. 2000;100 (9):1074-1076.
95. van Hagen CC, Carbasius Weber E, van den Hurk TE, et al. Energy expenditure in patients with propionic and methylmalonic acidemias. *J Inherit Metab Dis*. 2004;27(1):111-112.
96. Hauser NS, Manoli I, Graf JC, Sloan J, Venditti CP. Variable dietary management of methylmalonic acidemia: metabolic and energetic correlations. *Am J Clin Nutr*. 2011;93(1): 47-56.
97. Blecker U, de Meirleir L, de Raeve L, Ramet J, Vandenplas Y. Acrodermatitis-like syndrome in organic aciduria. *Pediatrics*. 1994;93(3):537.
98. Lane TN, Spraker MK, Parker SS. Propionic acidemia manifesting with low isoleucine generalized exfoliative dermatosis. *Pediatr Dermatol*. 2007;24:508-510.
99. Rosa J, Fraga AB, de Carvalho R, Maia AL, Rodrigues AL, Gomes MF. Acrodermatitis dysmetabolica as a sign of methylmalonic aciduria decompensation. *Clin Case Rep*. 2018;6(6): 1048-1050.
100. Tabanlioglu D, Ersoy-Evans S, Karaduman A. Acrodermatitis enteropathica-like eruption in metabolic disorders: acrodermatitis dysmetabolica is proposed as a better term. *Pediatr Dermatol*. 2009;26:150-154.
101. Bodemer C, de Prost Y, Bachollet B, et al. Cutaneous manifestations of methylmalonic and propionic acidaemia: a description based on 38 cases. *Br J Dermatol*. 2011;131(1):93-98.
102. Karamizadeh Z, Dalili S, Karamifar H, Hossein Amirhakimi G. Association of methylmalonic acidemia and erythema nodosum. *Iran J Med Sci*. 2011;36(1):65-66.
103. Al-Rikabi AC, Al-Homsi HI. Propionic acidemia and zinc deficiency presenting as necrolytic migratory erythema. *Saudi Med J*. 2004;25(5):660-662.
104. Bassim CW, Wright JT, Guadagnini JP, et al. Enamel defects and salivary methylmalonate in methylmalonic acidemia. *Oral Dis*. 2009;15:196-205.
105. Koopman WJH, Willems PHGM, Smeitink JAM. Monogenic mitochondrial disorders. *N Engl J Med*. 2012;366: 1132-1141.
106. Maguire CA, Chong H, Ramachandran R, Popoola J, Akhras V, Singh M. Acrodermatitis acidaemica. *Clin Exp Dermatol*. 2018; 43(3):315-318.
107. Nizon M, Ottolenghi C, Valayannopoulos V, et al. Long-term neurological outcome of a cohort of 80 patients with classical organic acidurias. *Orphanet J Rare Dis*. 2013;23(8):148.
108. O'Shea CJ, Sloan JL, Wiggs EA, et al. Neurocognitive phenotype of isolated methylmalonic acidemia. *Pediatrics*. 2012;129(6): e1541-e1551.
109. Pena L, Burton BK. Survey of health status and complications among propionic acidemia patients. *Am J Med Genet A*. 2012; 158A(7):1641-1646.
110. Radmanesh A, Zaman T, Ghanaati H, Molaei S, Robertson RL, Zamani AA. Methylmalonic acidemia: brain imaging findings in 52 children and a review of the literature. *Pediatr Radiol*. 2008; 38(10):1054-1061.
111. de Raeve L, De Meirleir L, Ramet J, Vandenplas Y, Gerlo E. Acrodermatitis enteropathica-like cutaneous lesions in organic aciduria. *J Pediatr*. 1994;124:416-420.
112. Rafique M. Propionic acidemia: demographic characteristics and complications. *J Pediatr Endocrinol Metab*. 2013;26(5–6):497-501.
113. Romano S, Valayannopoulos V, Touati G, et al. Cardiomyopathies in propionic aciduria are reversible after liver transplantation. *J Pediatr*. 2010;156:128-134.
114. Scott Schwoerer J, Clowes Candadai S, Held PK. Long-term outcomes in Amish patients diagnosed with propionic acidemia. *Mol Genet Metab Rep*. 2018;16:36-38.
115. Shuaib T, Al-Hashmi N, Ghaziuddin M, et al. Propionic acidemia associated with visual hallucinations. *J Child Neurol*. 2012;27: 799-803.
116. Sipahi T, Yilmaz D, Tavil B. Propionic acidemia with myelodysplasia and neutropenia in a Turkish child. *J Pediatr Hematol Oncol*. 2004;26:154-155.
117. Tu WJ. Methylmalonic acidemia in mainland China. *Ann Nutr Metab*. 2011;58:281.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Haijes HA, Jans JJM, Tas SY, Verhoeven-Duif NM, van Hasselt PM. Pathophysiology of propionic and methylmalonic acidemias. Part 1: Complications. *J Inherit Metab Dis*. 2019;42:730–744. https://doi.org/10.1002/jimd.12129