Journal of Inherited Metabolic Disease
https://doi.org/10.1007/s10545-017-0135-2

REVIEW

Organic acidurias in adults: late complications and management

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Received: 20 September 2017 / Revised: 5 December 2017 / Accepted: 28 December 2017

Abstract

Organic acidurias (synonym, organic acid disorders, OADs) are a heterogenous group of inherited metabolic diseases delineated with the implementation of gas chromatography/mass spectrometry in metabolic laboratories starting in the 1960s and 1970s. Biochemically, OADs are characterized by accumulation of mono-, di- and/or tricarboxylic acids ("organic acids") and corresponding coenzyme A, carnitine and/or glycine esters, some of which are considered toxic at high concentrations. Clinically, disease onset is variable, however, affected individuals may already present during the newborn period with life-threatening acute metabolic crises and acute multi-organ failure. Tandem mass spectrometry-based newborn screening programmes, in particular for isovaleric aciduria and glutaric aciduria type 1, have significantly reduced diagnostic delay. Dietary treatment with low protein intake or reduced intake of the precursor amino acid(s), carnitine supplementation, cofactor treatment (in responsive patients) and nonadsorbable antibiotics is commonly used for maintenance treatment. Emergency treatment options with high carbohydrate/glucose intake, pharmacological and extracorporeal detoxification of accumulating toxic metabolites for intensified therapy during threatening episodes exist. Diagnostic and therapeutic measures have improved survival and overall outcome in individuals with OADs. However, it has become increasingly evident that the manifestation of late disease complications cannot be reliably predicted and prevented. Conventional metabolic treatment often fails to prevent irreversible organ dysfunction with increasing age, even if patients are considered to be "metabolically stable". This has challenged our understanding of OADs and has elicited the discussion on optimized therapy, including (early) organ transplantation, and long-term care.

Keywords Organic acidurias · Methylmalonic aciduria · Propionic aciduria · Isovaleric aciduria · Glutaric aciduria type 1 · Clinical phenotype · Outcome · Management · Adults

Abbreviations

CNS	Central nervous system
CRF	Chronic renal failure
EO	Early (i.e. neonatal) disease onset
GA1	Glutaric aciduria type 1
IVA	Isovaleric aciduria
LO	Late disease onset (i.e. after the newborn period)
MRI	Magnetic resonance imaging
MMA	Isolated methylmalonic aciduria
OAD(s)	Organic aciduria(s)
PA	Propionic aciduria
QT_c	Corrected QT interval

Communicated by: Manuel Schiff

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Introduction

Organic acidurias (OADs) are a heterogeneous group of inherited metabolic diseases most often caused by inherited deficiency of enzymes involved in the degradation of amino acids resulting in the accumulation of so-called "organic acids", i.e. mono-, di- or tricarboxylic acids, which can be detected in body fluids. Some organic acids and accompanying acyl-CoA esters are thought to be toxic if they reach a critical threshold (Sauer et al 2008). Pathophysiologic concepts include disturbed brain energy metabolism and entrapment of dicarboxylic toxic metabolites in the brain compartment (Sauer et al 2005; Sauer et al 2006; Lamp et al 2011), activation of glutamatergic signaling (Kolker et al 2002), dysregulation of cerebral blood flow and endothelial cell dysfunction

Published online: 15 January 2018

(Muhlhausen et al 2006; Strauss et al 2010) in glutaric aciduria type 1 (GA1); inhibition and impairment of glycolysis and tricarboxylic acid cycle enzymes and respiratory chain complexes (Okun et al 2002; Melo et al 2011; Tuncel et al 2015) as well as disturbed ureagenesis due to inhibition of N-acetylglutamate synthase in isolated methylmalonic (MMA), propionic (PA) and isovaleric acidurias (IVA) (Coude et al 1979; Coude et al 1982; Schwab et al 2006). These pathomechanistic concepts may explain the acute manifestations of OADs, such as acute metabolic crises in MMA, PA and IVA as well as the acute or insidious onset of striatal damage in GA1, but are insufficient to explain disease progression and late complications.

With the exception of patients with GA1 who develop striatal damage mostly between the age of 3–36 months (Strauss et al 2003; Kolker et al 2006), patients with so-called "classic" OADs, i.e. MMA, PA and IVA may already present with first life-threatening symptoms shortly after birth. However, the age of disease onset is variable. Recent studies report that the proportion of individuals with late disease onset seems to be higher than initially suggested (Kolker et al 2015a, b). Furthermore, an increasing number of reports highlight that disease progresses even in patients who have not had any acute metabolic decompensation for years (or at all) and who were thought to be "metabolically stable" under conventional metabolic therapy (Martin-Hernandez et al 2009; Fraser and Venditti 2016).

The major aim of this review is to describe the evolving phenotypic spectrum of OADs and progression of symptoms in adolescents and adults in the light of potential consequences for long-term management. A precise understanding of the phenotypic development and variability and identification of parameters that reliably predict specific disease variants and late complications are prerequisites to adapt and improve long-term management and clinical outcome and to stimulate research.

Isolated methylmalonic aciduria

Isolated methylmalonic aciduria (MMA) comprises a heterogeneous group of autosomal recessively inherited disorders of propionate metabolism. The estimated overall incidence is one in 50,000 newborns (Baumgartner et al 2014). MMA is caused by reduced activity of the mitochondrial enzyme methylmalonyl-CoA mutase (EC 5.4.99.2) causing mut-type MMA (OMIM #251000) or by defects in the synthesis of its cofactor adenosylcobalamin (*cblA*-type MMA, MIM #251100; *cblB*-type MMA, MIM #251110; *cblD*-variant 2, MIM #277410) (Fowler et al 2008). Methylmalonyl-CoA mutase converts methylmalonyl-CoA to succinyl-CoA within the final catabolic pathway of L-isoleucine, L-valine, L-methionine, L-threonine, odd-chain fatty acids and the side chain of cholesterol. MMA is biochemically characterized by accumulation of methylmalonic acid and, due to activation of alternative pathways of propionate oxidation, by accumulation of propionate, 3-hydroxypropionate and 2-methylcitrate, all deriving from propionyl-CoA (Fenton et al 2001).

Clinical presentation

The onset of first symptoms ranges from the neonatal period to adulthood resulting in a subdivision of individuals with early (EO, ≤ 28 days) and late disease onset (LO, > 28 days) reflecting variable clinical severity (Deodato et al 2006; Kolker et al 2015a, b). In contrast to the EO form, which is usually associated with a severe disease course, the clinical spectrum of the LO form is more variable ranging from life-threatening metabolic decompensations to fluctuating or chronic symptoms. Clinical symptoms, acute or chronic, may mimic other conditions involving the central nervous system (CNS), gastrointestinal system, hematological system, heart and kidneys (Baumgartner et al 2014). In both onset types, patients suffer a life-long risk of recurrent metabolic decompensations that are often precipitated by catabolism, infectious diseases or excessive protein intake (Baumgartner et al 2014). Of note, some individuals with MMA may not develop a single metabolic decompensation during their whole life but present with feeding difficulties, cognitive disability, and dysfunction of heart and kidneys (Kolker et al 2015a, b).

Long-term complications

Since long-term survival has improved, progressive multiple organ dysfunction resembling disorders of oxidative phosphorylation is becoming more and more evident, even in individuals assumed to be "metabolically stable" (Dionisi-Vici et al 2006; Horster et al 2007; Kolker et al 2015a, b). Chronic inhibition of pyruvate dehydrogenase complex, tricarboxylic acid cycle enzymes and respiratory chain complexes induced by synergistically acting mitochondrial toxins, especially propionyl-CoA and 2-methylcitric acid, is thought to induce chronic impairment of mitochondrial energy metabolism, altered auto−/mitophagy and chronic mitochondrial dysfunction which is reflected by progressive formation of megamitochondria, diminished activity of cytochrome *c* oxidase and reduced intracellular glutathione and finally results in organ dysfunction (Morath et al 2008; Morath et al 2013; Ruppert et al 2015).

The brain – The brain is the most vulnerable organ in OADs. Neurological complications are frequent and often include non-specific features such as neurodevelopmental delay, intellectual disability, epilepsy and psychiatric disorders (Baumgartner et al 2014). Bilateral lesions of basal ganglia, in particular of globus pallidus, classically

occurring during acute metabolic decompensation and often termed "metabolic stroke", result in movement disorders, such as dystonia and chorea. Less frequently, brain atrophy and white matter abnormalities are identified by brain imaging (Radmanesh et al 2008; Baker et al 2015).

The intestinal tract – A likely underestimated long-term complication is pancreatitis, often with atypical presentation. The true prevalence of chronic or recurrent acute pancreatitis is unclear (Marquard et al 2011); however, individuals with chronic renal failure (CRF) are at increased risk (Pitchumoni et al 1996).

The heart – Cardiac involvement is a potentially severe long-term complication of MMA and may cause rapid deterioration or sudden death also in adulthood (Prada et al 2011). Less commonly than in PA but following the same pattern, life-threatening cardiac arrhythmias, particularly prolonged corrected QT interval (QT_c), hypertrophic or dilated cardiomyopathy may develop (Fraser and Venditti 2016). Heart failure can also occur in the absence of cardiomyopathy (Azar et al 2007).

The kidney – CRF is a frequent complication (Morath et al 2013). In isolated MMA, the risk of CRF can be predicted by three parameters: (1) the underlying enzymatic defect (mut^0, $cblB > cblA$, mut^-), the urinary concentration of methylmalonic acid before CRF (de Rivero Vaccari et al, 2016) and cobalamin responsiveness (Horster et al 2007; Horster et al 2009). CRF occurs even in mildly affected and "metabolically stable" patients requiring hemodialysis or kidney transplantation in adulthood (Haarmann et al 2013). Parenteral treatment with hydroxocobalamin in cobalamin-responsive patients (Haarmann et al 2013), intensification of dietary therapy and close monitoring of therapy (Schmitt et al 2004) may slow down kidney dysfunction, but in the long run conventional metabolic therapy is unlikely to prevent the manifestation of CRF in individuals with increased risk.

The eye – Optic neuropathy has been reported in eight patients with MMA, but its true frequency may be underestimated. Age of onset ranged between 2 and 24 years (Martinez Alvarez et al 2016). Acute bilateral loss of vision has been described in two adults (Williams et al 2009; Traber et al 2011) and one adolescent patient with isolated MMA (Pinar-Sueiro et al 2010). Treatment trials with antioxidant drugs (coenzyme Q_{10} with or without vitamin E) in a limited number of individuals showed discrepant results (Williams et al 2009; Pinar-Sueiro et al 2010; Traber et al 2011).

Management

Recommendations for acute and long-term management have recently been published by an international expert group (Baumgartner et al 2014), which can be consulted for detailed advice. For acute metabolic crises in adults, glucose (4–6 g/kg BW/d) and L-carnitine (50–100 mg/kg BW/d) should be administered intravenously.

The aforementioned recommendations are particularly helpful for the management of pediatric patients. However, literature addressing management and needs of adult patients affected by MMA is still rare and incomplete (Martin-Hernandez et al 2009). It is crucial to highlight here that general supportive care is often the major and most important part of long-term management of adults with OADs. Most patients have a high burden of multisystemic health problems requiring multidisciplinary care, and most of them are not able to live independently (Martin-Hernandez et al 2009). Mood disorders have to be anticipated and treated in this age group (Baumgartner et al 2014). In addition education and employment issues, independent housing, appropriate physiotherapy, medical needs, such as hearing or speech aids, and regular follow-up appointments (e.g. neurologic, cardiologic, endocrinologic, ophthalmologic, dental/oral care etc.) should be adapted according to the individual requirements. Every patient should also be given an emergency card containing measures to be taken in acute situations.

In combination with secondary hyperparathyroidism due to CRF there is a high risk of osteoporosis and pathological fractures. The use of antiresorptive medications such as bisphosphonates and diagnostic tools (e.g. dual energy X-ray) are not systematically evaluated in this particular patient group; therefore, treatment has to be tailored individually (Baumgartner et al 2014).

Organ transplantation

The high burden of long-term complications has led to an intensive debate regarding liver, combined liver-kidney or kidney transplantation and the best timing (Sloan et al 2015). Most evidence is based on case reports; only one larger series on liver and combined liver transplantation is available (Niemi et al 2015) and a smaller case series on kidney transplantation (Brassier et al 2013). Therefore, more systematic studies addressing who, when and which organs (liver, kidney, combined liver/kidney) should be transplanted are needed.

Pregnancy

Pregnancies in MMA patients are often complicated by cesarean delivery and increased risk of prematurity (Raval et al 2015), but with early diagnosis through newborn screening and improved pediatric care normal pregnancy, delivery and fetal outcome can be achieved more frequently (Jacquemyn et al 2014). The use of carnitine and high-dose cobalamin treatment (in cobalamin-responders) is considered safe (Deodato et al 2006; Martin-Hernandez et al 2009). A

teratogenic effect of MMA is not apparent, however, reports on pregnancies are still scarce. Langendonk et al (2012) reported on two pregnancies; one had no abnormalities and the other showed intrauterine growth retardation but with normal postnatal development.

Outcome and prognosis

The overall long-term outcome of individuals with isolated MMA often remains poor and is influenced by the onset type, enzymatic defect and cobalamin responsiveness. In general, cobalamin-responsive patients (mainly *CblA*-type MMA) have a much better outcome than non-responders (Nizon et al 2013; Baumgartner et al 2014; Kolker et al 2015a, b). CRF in particular, i.e. in *mut*^{0}- and *CblB*-type MMA, plays an important role with increasing age and has a negative impact on survival (Kolker et al 2015a, b). In summary, the long-term outcome of MMA is still unknown and there is uncertainty about the risk of developing (multiple) organ dysfunction with increasing age and about optimal long-term management in adult patients (Kolker et al 2015a, b).

Propionic aciduria

Propionic aciduria (PA, OMIM #606054) is an autosomal recessive OAD caused by deficiency of biotin-dependent propionyl-CoA carboxylase (EC 6.4.1.3) due to pathogenic genetic variations in *PCCA* (OMIM #232000) and *PCCB* (OMIM #232050) encoding subunits A and B (Ugarte et al 1999). Propionyl-CoA carboxylase catalyzes the carboxylation of propionyl-CoA to D-methylmalonyl-CoA upstream of methylmalonyl-CoA mutase, which explains the overlapping biochemical and clinical phenotypes of PA and MMA patients. The estimated overall incidence of PA is one in 100–150,000 newborns (Baumgartner et al 2014; Shchelochkov et al 2016). Higher incidences are found in Arabic countries (Moammar et al 2010) and the Inuit population of Greenland (Ravn et al 2000).

Clinical presentation, long-term complications and management

In analogy to MMA, individuals with PA can also be distinguished by EO and LO variants, and many long-term disease complications follow a similar pattern. However, the frequency of cardiac and renal manifestations is different (Deodato et al 2006; Kolker et al 2015a, b).

CNS – The brain is the most frequently affected organ; symptoms occur acutely during so-called "metabolic stroke" or chronically. Most common clinical findings are intellectual disability, movement disorders and epilepsy (Fraser and Venditti 2016). An association with autism spectrum disorders and PA was reported (Witters et al 2016).

The kidney – In contrast to MMA patients, CRF is usually not found in pediatric PA patients, and the first reports about this complication were published just a few years ago. The first reported PA patient with CRF was 42 years old (Lam et al (2011) and underwent kidney transplantation. A causal link between PA and CRF remained unclear before additional patients with CRF were identified (Vernon et al 2014; Kolker et al 2015a, b).

The heart – One of the clinically most relevant complications of PA is dilated or, less frequently, hypertrophic cardiomyopathy (Mardach et al 2005). Cardiomyopathy may deteriorate despite pharmacotherapy, but may be reversible following liver transplantation (Romano et al 2010; Arrizza et al 2015). Prolonged QT_c interval is the most frequent cardiac manifestation in PA. Therapy with β-blockers should be considered (Kakavand et al 2006; Baumgartner et al 2007; Jameson and Walter 2008; Rodriguez-Gonzalez and Castellano-Martinez 2016). Inhibition of the KvLQT1/KCNE1 potassium channel by toxic metabolites with concomitant prolongation of action potentials in cardiomyocytes is a potential pathomechanism (Rodriguez-Gonzalez and Castellano-Martinez 2016; Grunert et al 2017). Furthermore, coenzyme Q_{10} depletion may cause cardiac failure; thus, supplementation with coenzyme Q_{10} is discussed (Fragaki et al 2011).

The skeletal system – Independent from the renal status, patients are at increased risk of osteopenia or osteoporosis (Pena et al 2012). In contrast to MMA, fewer patients with PA suffer from pathological bone fractures (Martin-Hernandez et al 2009). Nevertheless routine scans with dual-energy X-ray absorptiometry is recommended (Fraser and Venditti 2016).

The eyes and the ears – Optic neuropathy, optic nerve atrophy, cataracts, ocular apraxia and bilateral sensorineural hearing loss have been described as long-term complications (Ianchulev et al 2003; Williams et al 2009; Pinar-Sueiro et al 2010; Arias et al 2014; Martinez Alvarez et al 2016). Whether supplementation therapy with coenzyme Q_{10} and vitamin E is beneficial remains to be elucidated (Martinez Alvarez et al 2016). One study has proposed pharmacologic modulation of potassium fluxes through KvLQT1/KCNE1, which is expressed in cardiomyocytes and the inner ear, as novel therapeutic strategy (Grunert et al (2017). However, a clinical study evaluating this concept has not been reported.

Similar to MMA, acute treatment of metabolic crises in adults comprise intravenous administration of glucose (4–6 g/kg BW/d) and L-carnitine (50–100 mg/kg BW/d).

Organ transplantation

Recommendations for metabolic treatment were published recently and, thus, are not discussed here (Baumgartner et al 2014). Since the description of long-term complications has challenged our view on the therapeutic ability to positively influence the metabolism of PA patients by conventional metabolic therapy, liver transplantation is increasingly discussed as a relevant alternative. In general, liver transplantation in PA patients should be regarded as supportive treatment that helps to normalize propionyl-CoA carboxylase activity in the liver, but not in other organs rather than curative treatment (Schlenzig et al 1995).

Although the first reports initially showed ambiguous results or even unsuccessful attempts in treating PA with liver transplantation (Schlenzig et al 1995; Leonard et al 2001), in recent years the number of patients with PA who have received a liver transplantation and reached a good outcome has increased (Barshes et al 2006; Rela et al 2007; Romano et al 2010; Vara et al 2011; Chapman et al 2012; Kasahara et al 2012; Fagiuoli et al 2013; Nagao et al 2013; Arrizza et al 2015; Charbit-Henrion et al 2015). Charbit-Henrion et al (2015) and other studies suggest that liver transplantation should be considered earlier in life, since younger organ recipients show better outcomes following liver transplantation probably as a result of a metabolic intoxication for a shorter period of time and a better nutritional status, whereas older recipients developed severe complications, such as hepatic artery thrombosis, cardiac or pulmonary insufficiency. Liver transplantation should be considered in patients with frequent episodes of hyperammonemia, metabolic crises and acute decompensations. CRF was observed as a complication following liver transplantation (Charbit-Henrion et al 2015). Whether this reflects an additive negative effect due to calcineurin inhibitor-mediated nephrotoxicity remains to be elucidated. In contrast, progression of cardiomyopathy in PA may be halted or even reversed after liver transplantation, which is unlikely to be achieved with conventional metabolic therapy (Romano et al 2010; Arrizza et al 2015).

Pregnancy

A few successful pregnancies of women with PA have been reported (Van Calcar et al 1992; Langendonk et al 2012; Van Calcar 2015; Scott Schwoerer et al 2016). Fetal development was considered as normal. To prevent metabolic crises or other negative effects of PA during pregnancy, it is of utmost importance that topics, such as pregnancy, contraception and sexual health, are discussed with women having PA in time and an individually adapted metabolic management is discussed and agreed in advance (Baumgartner et al 2014). As pregnancy represents a period with higher metabolic turnover and higher protein tolerance, dietary supplementation and medical therapy should be adapted to the individual needs requiring frequent follow-up appointments in a multiprofessional setting (Baumgartner et al 2014). The increase in cardiac output should also be monitored closely, e.g. with the help of an echocardiogram, to identify developing cardiomyopathies, which might lead to cardiac failure during or after pregnancy (Lewey and Haythe 2014).

Isovaleric aciduria

Isovaleric aciduria (IVA, OMIM # 243500) is a rare disorder of leucine metabolism with an estimated worldwide birth prevalence of 1:100,000 newborns diagnosed by newborn screening and 1:280,000 diagnosed after the onset of symptoms (Moorthie et al 2014). Pathogenic variations in the *IVD* gene on 15q15.1 encoding isovaleryl-CoA-dehydrogenase (EC 1.3.8.4) result in reduced enzyme activity and accumulation of isovaleryl-CoA and its derivates. Untreated patients are at risk of acute, often neonatal, metabolic crisis with acidosis and hyperammonemia leading to coma, severe neurological damage and death. However, the clinical presentation is variable. In analogy to MMA and PA, individuals are commonly divided into EO and LO groups. Thirdly, the implementation of newborn screening has unraveled a biochemically mild and clinically predominantly asymptomatic group of individuals with IVA, mostly associated with a common missense mutation c.932C > T (p.Ala282Val) (Ensenauer et al 2004). Besides this specific "mild" mutation, although, over 50 mutations in the *IVD* gene are known, genotype-phenotype correlation is, up to date, poorly understood (Vockley and Ensenauer 2006).

Clinical presentation and long-term disease outcome in adults

In 1966, Tanaka and co-workers (Tanaka et al 1966), described IVA as the first organic aciduria. In comparison to MMA and PA, individuals with IVA appear to have a less severe disease course. However, despite its delineation over 50 years ago the knowledge about long-term outcome and late complications in adult patients with IVA is still incomplete. Evidence-based recommendations are still missing.

Few studies reporting on the clinical phenotype comprise data of adolescent and adult patients. Systematic evaluation of 21 symptomatic IVA patients (age 2.2–25.3 years) and the available literature demonstrated higher mortality (33%) in the EO group, predominantly during the first neonatal decompensation, compared to the LO group (Grunert et al 2012). However, EO patients surviving the initial metabolic decompensation had a better neurocognitive outcome (82% unremarkable neurocognitive outcome) than LO patients (44%) (Grunert et al 2012). Recent publications from the European

registry and network for intoxication type metabolic diseases (E-IMD; https://www.eimd-registry.org) including adolescent and adult IVA patients [$n = 49$, age: 0.1–45.8 years (Kolker et al 2015a, b); $n = 83$, age 0.1–48.9 years (Heringer et al 2016)] confirmed clinical and neurocognitive outcome depend on early diagnosis and treatment in IVA. Symptomatic patients present with developmental delay, movement disorders and neurocognitive deficits; however, the majority of IVA patients had a normal clinical and neurocognitive outcome (Kolker et al 2015a, b; Heringer et al 2016).

In contrast to PA and MMA, there is no apparent disease progression in IVA patients (Martin-Hernandez et al 2009) and multisystemic organ dysfunction has not been described. Gastrointestinal symptoms, such as pancreatitis (Kahler et al 1994), vomiting, diarrhea and protein aversion, seem to be rare (Kahler et al 1994; Kolker et al 2015a, b) and do not affect growth (Kolker et al 2015a, b). In 21 symptomatic patients, no metabolic decompensation occurred after the age of 9 years (Grunert et al 2012). Nevertheless, single cases of adult metabolic decompensations have been reported (Feinstein and O'Brien 2003; Kimmoun et al 2008).

Management

IVA has been included in newborn screening programmes in an increasing number of countries (Loeber et al 2012; Horster et al 2017) allowing pre-symptomatic diagnosis for LO-type IVA patients, but is likely to also prevent neonatal decompensation in the majority of EO-type IVA patients (Heringer et al 2016). Presymptomatically diagnosed and treated individuals often remain asymptomatic until adolescence/adulthood. In many countries, however, there is still a need to establish a transition from pediatric to adult health care and long-term care to prevent a drop-out of medical care and to support lifelong compliance analogous to other inborn metabolic diseases (Mutze et al 2011; Mutze et al 2016). Although metabolic crisis occur rarely in adulthood, prolonged fasting and catabolic stress should be avoided life-long to prevent metabolic decompensations (Feinstein and O'Brien 2003) by oral or intravenous carbohydrate supply (4–6 g/kg BW/d) and if necessary additional carnitine supplementation (50–100 mg/kg BW/d). Patients, therefore, should also be equipped with an emergency card.

The safety and efficacy of pharmacological and dietary management of IVA in adolescence and adulthood has not yet been systematically studied, and there is a need for international harmonization of treatment strategies. Considerable variations in the dietary management and pharmacotherapy still exist worldwide, which increases the risk of over- and undertreatment (Heringer et al 2016; Pinto et al 2017).

In classical IVA (EO and LO onset), a protein-controlled diet (according to the WHO recommendation for safe daily protein intake) avoiding excessive protein intake is currently more often used than a low leucine diet with leucine-free amino acid supplements reflecting that over the years dietary management has become more and more relaxed for IVA patients. Carnitine supplementation is recommended as life-long therapy to prevent secondary carnitine depletion and promote the formation of isovalerylcarnitine. In contrast, the effect of additional glycine supplementation, which provides an alternative strategy for the esterification of toxic isovaleryl-CoA, remains controversial.

In asymptomatic individuals with mild IVA, indication for preventive therapy is uncertain. To date, prevention of metabolic crisis by patients' education and equipment with an emergency card and, if necessary, low dose carnitine supplementation is recommended (Vockley and Ensenauer 2006). However, no metabolic crises in patients with mild IVA have been reported yet.

Pregnancy

Several pregnancies of women with IVA were reported, without evidence for teratogenicity (Spinty et al 2002; Castelnovi et al 2010; Habets et al 2012). Outcome for mother and child appear to be good. Special needs during pregnancy, i.e. sufficient protein, vitamin and carnitine intake, should be monitored and catabolic stress, especially during labor and involution of the uterus, should be covered by intravenous glucose (Habets et al 2012).

Glutaric aciduria type 1

Glutaric aciduria type 1 (GA1, OMIM #231670) is a rare autosomal recessive disorder of L-lysine, L-tryptophan and L-hydroxytryptophan metabolism with an estimated incidence of 1:110,000 newborns (Kolker et al 2007). Inherited deficiency of glutaryl-CoA dehydrogenase (EC 1.3.8.6) results in accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid and non-toxic glutarylcarnitine. Since untreated patients develop severe irreversible neurologic symptoms, GA1 has been termed a 'cerebral' organic aciduria, but the clinical phenotype is still evolving.

Two biochemical subtypes, i.e. low and high excretors, were defined arbitrarily based on the amount of urinary glutaric acid excretion (Baric et al 1999) and inversely correlate with residual enzyme activity. Both subgroups were thought to share the same clinical course in infancy and childhood (Christensen et al 2004; Kolker et al 2006), which has been explained by entrapment and subsequent accumulation of neurotoxic dicarboxylic metabolites in the brain compartment (Sauer et al 2006). However, recent studies unraveled a higher frequency of white matter abnormalities and increased concentrations of neurotoxic metabolites progressing with age

in high excretors compared to low excretors (Harting et al 2015). The clinical relevance of this finding is still unclear.

Clinical presentation and long-term complications

Neonates and infants may present with unspecific and transient neurologic symptoms like muscular hypotonia; 75% of them are macrocephalic. Subdural hemorrhage may occur following minor head trauma (Brismar and Ozand 1995; Vester et al 2016) and may be mistaken as the result of abusive head trauma (Morris et al 1999; Vester et al 2015). Noteworthily, subdural hemorrhage may also manifest in early diagnosed and treated children without macrocephaly (Zielonka et al 2015).

Striatal damage and complex movement disorder with predominant dystonia – Over 90% of untreated patients develop a complex movement disorder with predominant dystonia, mostly between the age of 3–36 months, but not after the age of 6 years, indicating a window of vulnerability. Onset of dystonia may be *acutely* during an encephalopathic crisis precipitated by catabolism and infectious diseases or *insidiously* and is the clinical correlate of bilateral striatal necrosis (Kolker et al 2006; Harting et al 2009). Insidious onset of symptoms has been increasingly observed in neonatally diagnosed individuals not adhering to dietary recommendations (Heringer et al 2010). Overall, the severity of the acquired movement disorder and motor disability remains stable with increasing age. However, dystonia, superimposed on axial hypotonia, tends to become fixed and to be associated with akinetic-rigid parkinsonism with age. Orofacial involvement often results in dysarthria and speech apraxia. Treatment of dystonia is difficult and often frustrating; baclofen and trihexiphenidyl are frequently used for generalized dystonia and botulinum toxin A for focal dystonia (Gitiaux et al 2008). The risk of epilepsy is increased and might even be the initial presentation (McClelland et al 2009; Kolker et al 2015a, b). Cognitive functions, however, seem to be preserved in most individuals with GA1, even after striatal damage (Boy et al 2015).

Extrastriatal manifestations – Besides *acute* and *insidious* onset of motor symptoms, patients with supposedly *late onset* of symptoms, i.e. presenting with first symptoms *after* the window of vulnerability for striatal damage, have also been described. The first report described a 19-year-old patient with headache, nystagmus, upward gaze palsy, fine motor disturbances and periventricular white matter T2 hyperintensity (Bahr et al 2002). In the following years, additional patients aged 8–71 years were published (Kulkens et al 2005; Fraidakis et al 2015; Pierson et al 2015; Boy et al 2017a, b). A variety of non-specific general and neurologic symptoms, such as headaches, nausea, vertigo, nystagmus, dysarthria, hyper- or hypoactive tendon reflexes, muscular weakness, transient ataxia or fine motor deficits, were reported. Older patients seemed to have more severe neurologic symptoms including progressive dementia, tremor and focal epilepsy (Boy et al 2017a, b). In addition, six asymptomatic adult female patients with uneventful pregnancy and delivery were diagnosed following initially abnormal newborn screening results of their children (Crombez et al 2008; Garcia et al 2008; Vilarinho et al 2010; Boy et al 2017a, b). Crombez et al (2008) and Garcia et al (2008) reported that high levels of glutaric acid or 3-hydroxyglutaric acid in pregnant patients have no significant effects on the newborns, although neuroimaging showed slightly delayed maturation of these newborns. It is noteworthy that all reported patients with late manifestation of symptoms were high excretors and did *not* develop striatal necrosis. Low-excreting patients with late onset of symptoms have not been reported so far. All *late-onset* GA1 patients commonly show extrastriatal abnormalities on brain MRI such as frontotemporal hypoplasia (as the most common and characteristic MRI finding in these patients) and white matter changes (also found in *acute* or *insidious* onset type patients and apparently increasing with age). In addition, subependymal lesions occurred in patients older than age 12 years and in one early treated patient (Kulkens et al 2005; Korman et al 2007; Herskovitz et al 2013; Pierson et al 2015; Boy et al 2017a, b). These lesions are predominantly located at the roof of the lateral ventricles and their number and size slowly increase with age. However, histopathology was not reported and, therefore, the etiology of these lesions still remains unclear. It has been reported that neurotoxic metabolites accumulate in the brain due to limited flux of dicarboxylic acids across the blood-brain barrier (Sauer et al 2006; Boy et al 2017a, b). Therefore, it has been hypothesized that extrastriatal changes in *late-onset* GA1 might reflect cumulative, chronic neurotoxicity in untreated patients with a high-excreting phenotype. However, these patients are not categorically different from early treated patients (Sauer et al 2006; Boy et al 2017a, b).

Extracerebral and non-neurologic manifestations – Recently, it was demonstrated that the disease manifestation of GA1 is not strictly limited to the CNS. One adult patient with peripheral polyneuropathy has been reported highlighting that *extracerebral* manifestations like peripheral nervous system might also be involved in long-term disease course (Herskovitz et al 2013). As the first *extraneurologic* manifestation, renal disease might also contribute to long-term complications (Kolker et al 2015a, b). In a few adults with GA1, compensated CRF was found and did not correlate with the neurological phenotype. In contrast to other OADs, none of these patients underwent hemodialysis. Renal disease in GA1 had also been reported in pediatric patients (Poge et al 1997;

Pode-Shakked et al 2014; du Moulin et al 2017). In a GA1 mouse model, tubular dysfunction and altered mitochondrial morphology have been observed during induced metabolic crises (Thies et al 2013), and toxic dicarboxylic metabolites are thought to negatively influence the transport of dicarboxylic acids in proximal tubule cells (Stellmer et al 2007).

Management

GA1 has been included into newborn screening programmes in many countries (Loeber et al 2012; Horster et al 2017). Early diagnosis is the prerequisite of effective treatment and favourable outcome. Metabolic treatment comprises low lysine diet with supplementation of lysine-free, tryptophan-reduced, arginine-containing amino acid mixture, carnitine supplementation (30–50 mg/kg BW/d), intravenous glucose (4–6 g/kg BW/d) and intensified emergency treatment during catabolic episodes. Several studies in different countries confirmed a favourable outcome if (1) diagnosis was made and treatment was started neonatally, (2) metabolic treatment followed current recommendations and (de Rivero Vaccari et al, 2016) patients were followed by a multiprofessional team of experts (Naughten et al 2004; Kolker et al 2006; Kolker et al 2007; Heringer et al 2010; Strauss et al 2011; Viau et al 2012; Couce et al 2013; Lee et al 2013). Based on this, evidence-based recommendations have been revised recently (Boy et al 2017a, b).

Effectiveness of dietary treatment after 6 years has not been systematically studied. Dietary protocol might be relaxed in this age group and should be based on *protein control* using natural protein with a low lysine content and avoidance of lysine-rich food since evidence for chronic neurotoxicity is increasing (Harting et al 2015; Boy et al 2017a, b). Carnitine should be supplemented lifelong. Since a positive effect of treatment on the extrastriatal MRI abnormalities has not yet been demonstrated, treatment recommendations for high- and

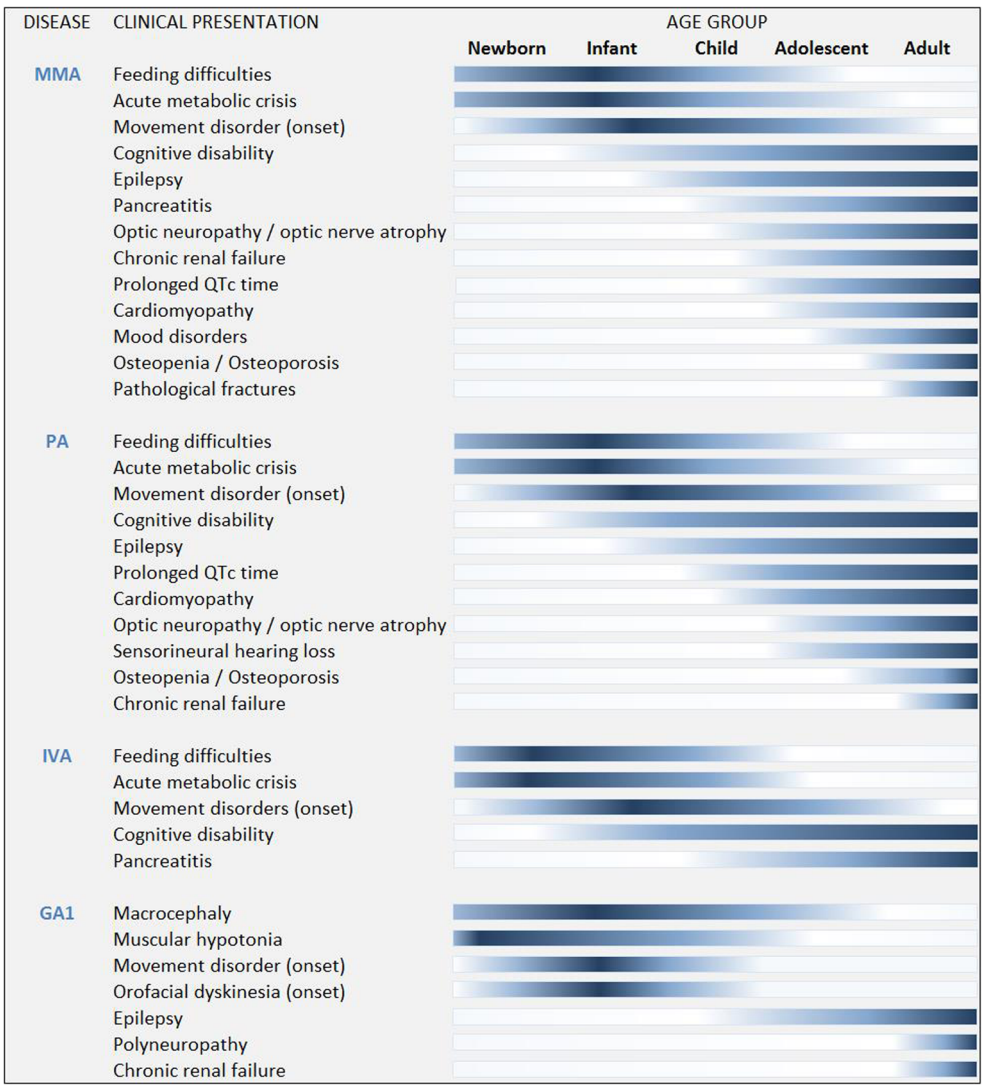

Fig. 1 Age-dependent and organ-specific disease manifestation in organic acidurias. The synopsis shows the age groups at which organ-specific symptoms are characteristically found or manifest in individuals with different organic acidurias. Some manifestations are less frequently found with increasing age (e.g. acute metabolic crisis, feeding difficulties), whereas others persist or aggravate over time (e.g. movement disorder) or are only found in older age groups (e.g. mood disorder). The figure does not refer to the relative or absolute frequency of the depicted clinical presentations

low-excreting patients are the same (Boy et al 2017a, b). Further studies are needed to evaluate differences in the risk profiles of biochemical subtypes and the stratification of treatment. Pharmacologic modulation of lysine oxidation appears to be a therapeutic option but recent attempts to inhibit Dhtkd1 (Dehydrogenase E1 and Transketolase Domain Containing 1) failed to rescue the biochemical and clinical phenotype of Gcdh-deficient mice, an animal model with complete loss of glutaryl-CoA dehydrogenase activity (Biagosch et al 2017).

Outlook

As a consequence of increased awareness, improved diagnostic and therapeutic options, an increasing number of individuals with OADs reach adulthood. However, it has become increasingly evident that adolescent and adult patients often face progressive (multiple) organ manifestations despite an early start of metabolic treatment and that long-term complications are also observed in supposedly "metabolically stable" patients. Figure 1 provides an overview on age-dependent and organ-specific disease manifestations in OADs.

These new findings challenge our view on the natural history and long-term outcome as well as efficacy and safety of current treatment strategies and highlight the need for systematic observational and interventional studies and, finally, the development of improved treatment and care concepts. To overcome these current limitations is the next giant leap for OADs, as for most other—if not all—inherited metabolic diseases. The establishment of European and international networks such as the European registry and network for Intoxication type Metabolic Diseases (E-IMD) and the European Reference Network for Hereditary Metabolic Diseases (MetabERN) is an important prerequisite to systematically collect natural history and outcome data, to initiate a multi-stakeholder approach to these rare diseases, to empower patients and their families and to harmonize diagnosis, treatment and care, and finally, to improve the health and quality of life of individuals with OADs and other inherited metabolic diseases.

Compliance with ethical standards

Conflict of interest A. T. Tuncel, N. Boy, M. A. Morath, F. Hörster, and U. Mütze declare that they have no conflict of interest.

Stefan Kölker has received speaker honorarium from Vitaflo, Nutricia (Danone group) and Orphan Europe (Recordati group) and has received project grants from Horizon Pharma International Limited and Orphan Europe SARL (Recordati group).

Informed consent Not applicable.

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

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