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REVIEW ARTICLE

Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature

A. Schlune[1] · S. vom Dahl[2] · D. Häussinger[2] · R. Ensenauer[1] · E. Mayatepek[1]

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Abstract Hyperargininemia is caused by deficiency of arginase 1, which catalyzes the hydrolysis of L-arginine to urea as the final enzyme in the urea cycle. In contrast to other urea cycle defects, arginase 1 deficiency usually does not cause catastrophic neonatal hyperammonemia but rather presents with progressive neurological symptoms including seizures and spastic paraplegia in the first years of life and hepatic pathology, such as neonatal cholestasis, acute liver failure, or liver fibrosis. Some patients have developed hepatocellular carcinoma. A usually mild or moderate hyperammonemia may occur at any age. The pathogenesis of arginase I deficiency is yet not fully understood. However, the accumulation of L-arginine and the resulting abnormalities in the metabolism of guanidine compounds and nitric oxide have been proposed to play a major pathophysiological role. This article provides an update on the first patients ever described, gives an overview of the distinct clinical characteristics, biochemical as well as genetical background and discusses treatment options.

Keywords Urea cycle · Arginase deficiency · Hyperargininemia · Guanidino compounds · Oxidative stress

✉ A. Schlune
andrea.schlune@med.uni-duesseldorf.de

[1] Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Heinrich Heine University, Moorenstr. 5, 40225 Düsseldorf, Germany

[2] Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, Heinrich Heine University, Moorenstr. 5, 40225 Düsseldorf, Germany

Abbreviations

AGAT	L-Arginine-glycine amidinotransferase
ASL	Argininosuccinate lyase
ASS	Argininosuccinate synthase
CSF	Cerebrospinal fluid
CPSI	Carbamoyl phosphate synthase I
GAA	Guanidinoacetate
GAMT	Guanidinoacetatemethyltransferase
GC	Guanidino compounds
NAGS	N-Acetyl-glutamate synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
ORNT1	Mitochondrial ornithine transporter
OAT	Ornithine aminotransferase
OTC	Ornithine transcarbamylase
UCD	Urea cycle disorder

Introduction

The urea cycle produces urea from ammonia and was the first metabolic cycle to be described (Krebs 1932). It consists of five consecutive enzymatic reactions distributed between the mitochondria [carbamoyl phosphate synthase 1 (CPS1) and ornithine transcarbamylase (OTC)] and the cytosol [argininosuccinate synthase (ASS), arginosininosuccinate lyase (ASL), and arginase] working together to detoxify waste nitrogen and synthesize L-arginine.

N-acetyl-glutamate synthase (NAGS) synthesizes *N*-acetylglutamate, an essential allosteric cofactor for CPSI, thereby controlling flux through the urea cycle (Caldovic et al. 2010). NAGS activity is induced by L-arginine in humans (Bachmann et al. 1982). In addition, two

transporters mediating the transport of urea cycle intermediates between mitochondria and cytosol are critical for maintenance of urea cycle functionality, the mitochondrial ornithine transporter ORNTI (Camacho et al. 1999) and the aspartate glutamate carrier (citrin) (Saheki et al. 2004; Fig. 1). The liver is the only organ in the human body to contain all enzymes needed for full function of the urea cycle. Human defects of all six enzymes as well as two transporters involved in the urea cycle are known. All urea cycle defects may result in accumulation of excess ammonia, resulting in acute or chronic neurological damage (Brusilow 2001).

Arginase was discovered in the mammalian liver in 1904 (Kossel 1904). Arginase 1 (L-arginine-urea-hydrolyase; EC 3.5.3.1) catalyzes the final step of the urea cycle, namely the hydrolysis of L-arginine to ornithine and urea. Urea can be excreted by the kidneys, whereas ornithine is returned to the mitochondria to continue the cycle. Arginase 1 deficiency (OMIM #207800) is inherited in an autosomal-recessive manner. It is one of the rarest urea cycle disorders (UCDs). 67 patients have been reported in the literature so far, and 22 have been recorded in the UCD Consortium's registry (Batshaw et al. 2014). Based on data from newborn screening records and the UCD Consortium's study, the incidence of arginase 1 deficiency has been estimated at about 1:950,000 (Summar et al. 2013), accounting for 3.5 % of all UCDs (Batshaw et al. 2014). Increased frequencies are found in the French–Canadian population due to a founder effect in Northern Quebec (Lemieux et al. 1988; Qureshi et al. 1983) and in Portugal (Martins et al. 2010).

Arginase 1 deficiency differs from the other UCDs that often present with dramatic hyperammonemic encephalopathy and coma already in the neonatal period. It typically manifests in late infancy or pre-school age with progressive spastic paraparesis, psychomotor and growth retardation, and epileptic seizures. Hepatic pathology such as neonatal cholestasis, acute liver failure, or liver fibrosis may also be present, and some patients have developed severe liver disease and hepatocellular carcinoma. A usually mild or moderate hyperammonemia may occur at any age.

We provide an update on the original first described patients, her natural history and present an overview of the distinct clinical characteristics, the biochemical and genetic background and discuss treatment options.

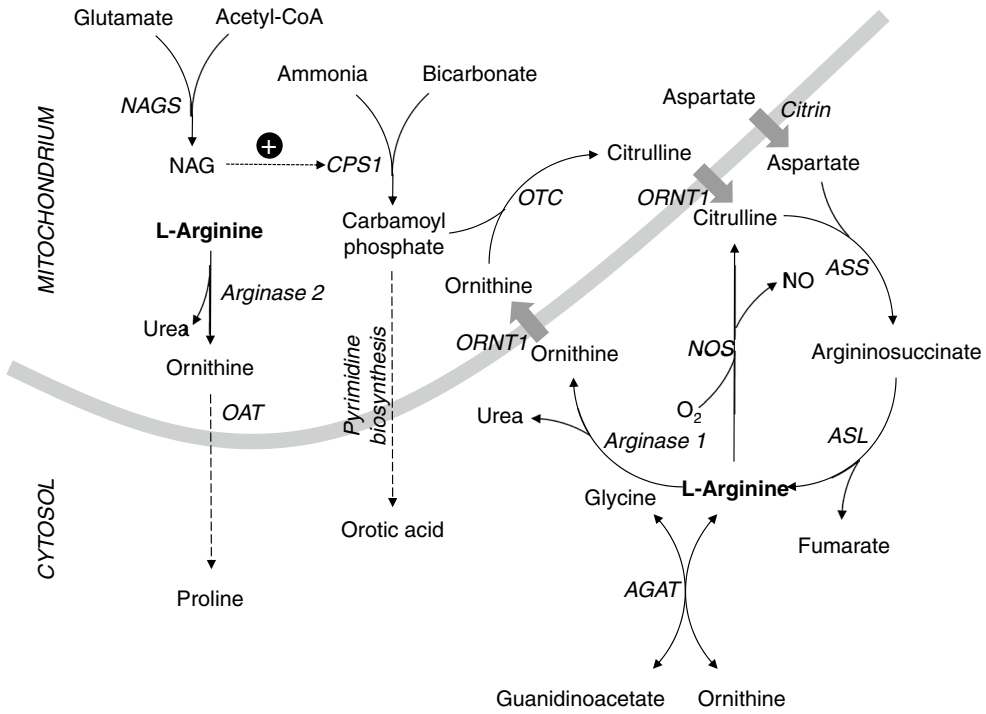


Fig. 1 L-Arginine metabolism in the urea cycle and related pathways. Arginase 1 cleaves L-arginine to urea which can be excreted by the kidneys and ornithine which is returned to the mitochondria to continue the urea cycle. L-Arginine can alternatively be converted into ornithine by L-arginine:glycine amidinotransferase (AGAT). In the same step, glycine is converted into guanidinoacetate in the creatine biosynthesis pathway. Different isoforms of nitric oxide (NO) synthase (NOS) synthesize NO and citrulline from L-arginine. Intramitochondrially located arginase 2 directs arginine to proline production via ornithine aminotransferase (OAT)

Patient reports

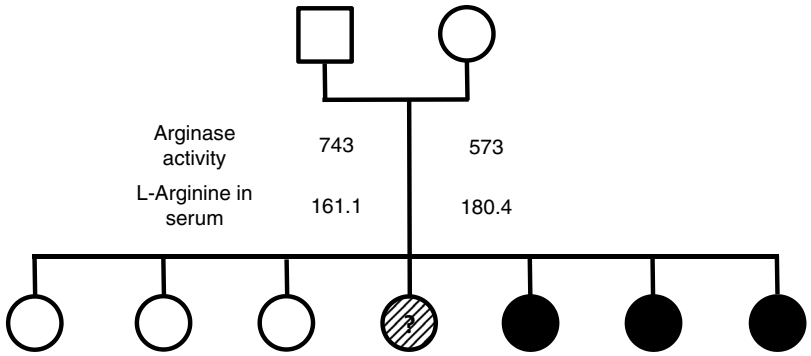
The patients presented here are the first three patients ever reported with hyperargininemia due to arginase I deficiency. Two sisters (patients E and F) were diagnosed at 5 years and 18 months of age, respectively (Terheggen et al. 1969, 1970a, b). A younger sister (pat. G) was diagnosed immediately after birth (Terheggen et al. 1975). For a complete pedigree, see Fig. 2.

Initial presentation

The oldest affected sister (patient E, *1964) was born as the fifth of seven girls to healthy, distantly consanguineous parents after an uneventful pregnancy. At 22 months of age, she presented with epileptic seizures. Abnormal gait was noticed when the girl was 2½ years old and, by the age of 3 years, spastic diplegia had developed. The middle sibling of the three affected girls (patient F, *1968) was born as the sixth girl of her parents. Cerebral seizures were noticed at 3 months of age. In the following months, periodic vomiting occurred and hepatomegaly and spasticity developed. Both girls showed psychomotoric retardation.

As the two children presented with nearly identical clinical features, specific tests were performed. A marked increase of L-arginine in serum and cerebrospinal fluid (CSF) was accompanied by a mild to moderate hyperammonemia and low-normal serum urea concentrations. Arginase analysis in red blood cells showed very low enzyme activity in both patients (120 µmol/h/g hemoglobin in the 5-year-old girl (patient E), almost undetectable in the 18-month-old girl (patient F, reference range in healthy control subjects: 793–1330 µmol/h/g hemoglobin). In both clinically inapparent parents, decreased arginase enzyme activities (mother 573 µmol/h/g hemoglobin, father: 743 µmol/h/g hemoglobin) and moderate elevations of L-arginine levels in serum were detected (Fig. 2). Therefore, an autosomal-recessive disorder with heterozygosity of the parents was assumed (Terheggen et al. 1969, 1970b). A reduction of protein intake to 1.5 g per kg body weight resulted in a decrease of blood ammonia levels; however, hyperargininemia persisted (Terheggen et al. 1969, 1970a, b).

Two elder, apparently healthy sisters (B, C) were also found to have moderate elevations of L-arginine whereas another elder sister (A) had normal L-arginine levels. Another elder sister (D) had died at 4 months of age because of pneumonia. It may be assumed that she also was



	A	B	C	D	E	F	G
	*1959	*1961	*1962	*1963 †4 months	*1964 † 2011	*1968 † 2013	*1971
Arginase activity	n.d.	n.d.	n.d.	n.d.	120	<50	<50
L-Arginine in serum before treatment	116.6	212.2	149.8	n.d.	640.0	1247.0	252.0* - 1579.2
L-arginine in serum under treatment					169-195	265-300	337-399

Fig. 2 Pedigree of the affected family. Seven children were born to healthy parents. Affected children (*e*, *f*, *g*) are given as *solid circles*, a potentially affected child who died aged 4 months and for whom no biochemical data are available is given as *hatched circle*. Arginase enzyme activities measured in red blood cells from peripheral blood are given in µmol/h/g Hb, reference range 793–1330, L-arginine serum levels before treatment are given in µmol/l, reference range 91.6 ± 22.5, *n.d.* not determined (Terheggen et al. 1969, 1975). *1st day of life

affected by arginase deficiency even though for her no biochemical data are available.

The youngest sister (patient G) of the two clinically affected girls (E, F) was diagnosed immediately after birth by elevation of L-arginine in cord blood and reduced arginase activity in red blood cells from cord blood as well as peripheral blood. A low-protein diet with 1.5 g per kg body weight per day was introduced at 8 weeks of age leading to a reduction of the serum arginine concentration to approximately 800 µmol/l. At 5 months of age, first motoric abnormalities were present, and at the age of 3 years she showed marked psychomotor retardation and spasticity of the lower extremities similar to her sisters, but seizures or EEG abnormalities were absent (Terheggen et al. 1975).

Treatment and outcome

The two younger patients (patients F and G) were first seen at the Düsseldorf University Childrens' Hospital when they were 14 and 11 years old, respectively. At that time, it was unclear how much protein per day the girls received, but there were signs of malnutrition with dystrophy and rickets in both of them. Therefore, both were started on a dietary regimen with a defined protein intake of 0.75–1 g per kg body weight per day. Both could not talk. The eldest affected sister (patient E) first presented to the Düsseldorf University Childrens' Hospital at the age of 25 years. At that time, she was able to walk short distances, talk and even write a few words. A cranial MRI was performed and showed no abnormalities.

When the patients presented again to the adult department later in adulthood, all were found to be severely underweight. Feeding difficulties persisted requiring percutaneous endoscopic gastrostomy for patients F and G. Treatment with sodium benzoate and sodium phenylbutyrate was started in all three patients to improve protein tolerance.

Over time, signs of liver fibrosis with inhomogeneous liver morphology and multiple hypoechogenic focal lesions as seen by ultrasound and a twofold elevation of liver enzymes were found in all three patients. Histologic workup was performed in one patient (patient G) and revealed severe steatohepatitis. It remains unclear whether this was related to the severe malnourishment which was present in all three patients or due to the underlying disease.

All three patients had ammonia levels which were within the normal range or only mildly elevated, but relapsing episodes of hyperammonemia with ammonia levels of around 350 µmol/l occurred in all three patients.

Cranial CT scans which were taken in the patients' thirties and forties showed diffuse widening of internal and external cerebrospinal spaces consistent with cerebral atrophy. In two patients (F and G), atrophy of the corpus callosum was shown.

Patient F was the most affected of the three sisters. Being tetraspastic, she was mentally severely retarded and had multiple flexion contractures. During her 45 years of life, she was constantly experiencing epileptic seizures, which were moderately controlled with levetiracetam and phenobarbital, requiring additional administration of phenytoin in 2013. After a continuous epileptic state and presentation with a subileus, she had to be admitted to an intensive care unit and died due to septic complications in 2013.

In spite of having been diagnosed immediately birth, like her elder sister (F), patient G was mentally severely retarded and was wheelchair-bound. Her permanent medication included sodium phenylbutyrate, sodium benzoate and a combined anticonvulsive medication. During epileptic seizures in 2007, she experienced traumatic maxillofacial fracture requiring osteosynthesis. During her last visit in 2013 at the age of 42 years, she was found to be in a stable clinical and metabolic state.

Interestingly, the oldest affected sister (patient E) primarily appeared to be the least affected one, even though she was diagnosed and treated later in life than her younger sisters (patients F and G). This might have been due to higher residual enzymatic activity and lower levels of L-arginine in serum before treatment (Terheggen et al. 1969), and the fact that she achieved lower levels of L-arginine in serum protein-restrictive treatment in early adulthood (169–195 µmol/l as compared to 265–300 µmol/l in patient F and 337–399 µmol/l in patient G). However, she finally developed epilepsy and spastic paraparesis and did no longer have control of bowels and urine. In her forties, she developed hyperthyroidism due to multifocal autonomy, which was treated by thyroidectomy. She lived in a nursery home until 2011 in a clinically and metabolically stable state. Her nutrition was maintained by a port-a-cath system. In 2011, she had to be acutely transferred to the University Hospital's ICU from an external clinic, being primarily on high-dose catecholamines due to septicemia because of bilateral pneumonia and a yet unknown intraabdominal abscess. The patient died because of septic shock after 24 h without a chance of a specific diagnostic or therapeutic approach. An autopsy was not performed.

Marked differences in phenotypic severity have also been reported for other siblings with comparable degrees of arginase deficiency (Prasad et al. 1997).

Pathophysiology and pathobiochemistry

The distinct clinical features of arginase 1 deficiency with progressive cerebral and motor neuron disorder not seen in other UCDs suggest that the underlying pathogenetic mechanisms are distinct from those occurring in other UCDs and

are related to elevated L-arginine levels, either directly or indirectly through alterations of L-arginine metabolites.

L-Arginine is a semi-essential amino acid which has numerous functions in the human body. It serves not only as an intermediate in the urea cycle, but is also a substrate for protein synthesis and a precursor to nitric oxide (NO), proline, polyamines, glutamate, creatine, and agmatine (Fig. 1; Morris 2007). Accumulation of L-arginine in arginase 1 deficiency was shown to activate alternative pathways of L-arginine degradation. In particular, the resulting abnormalities in the metabolism of guanidine compounds (GC) and NO have been proposed to play a major pathophysiological role.

L-Arginine:glycine amidinotransferase (AGAT) converts L-arginine into ornithine. In the same step, glycine is converted to guanidinoacetate (GAA). Elevated concentrations of GAA and other GC synthesized from L-arginine have been observed in body fluids and tissues of patients with arginase 1 deficiency (Terheggen et al. 1975; Marescau et al. 1985, 1990), and their concentrations have been shown to correlate with L-arginine levels (Deignan et al. 2010).

GC are well known to be epileptogenic (Hiramatsu 2003), probably due to impairment of gamma-aminobutyric acid and glycine responses in the CNS (De Deyn et al. 1991) and may be responsible for neurological damage in arginase 1 deficiency (Mizutani et al. 1987b; Wiechert et al. 1989). GC have also been shown to alter acetylcholinesterase and butyrylcholinesterase activities in rat brain cells (Delwing-de Lima et al. 2010). Some GC inhibit transketolase activity which might lead to demyelination and upper motor neuron signs (Lonergan et al. 1971).

Elevation of GAA plays an important pathophysiological role in guanidinoacetatemethyltransferase (GAMT) deficiency, an inborn error in the creatine biosynthesis pathway characterized by severe epilepsy (Stockler-Ipsiroglu et al. 2014). Reduction of GAA by L-arginine restriction and ornithine supplementation has been shown to lead to marked clinical improvement in a patient with GAMT deficiency and intractable seizures (Schulze et al. 2001).

NO contributes to myriad physiological processes, including signal transduction, neurotransmission, immune response mediation, and vasodilation. NO is an important modulator of neuronal function (Prast and Philippu 2001). At pathological levels, it adversely affects brain function by induction of oxidative stress (Wyse et al. 2004) and may promote the development of neurodegenerative diseases (Virarkar et al. 2013). L-Arginine is a substrate for NOS, and increased L-arginine levels have been associated with increased NO production (Buchmann et al. 1996; Wu and Morris 1998). L-Arginine has been shown to induce oxidative stress (Wyse et al. 2001) and decrease energy metabolism in brain (Delwing et al. 2003). L-Arginine-induced oxidative stress has been shown to inhibit the activity of Na^+, K^+-ATPase (dos Reis et al. 2002; da Silva et al. 1999), a transporter which is vital to maintain neuronal excitability (Delwing et al. 2008).

Arginase exists in two isoforms, arginase 1 and arginase 2 (reviewed in). Arginase 1 is cytosolically located and primarily found in liver and in red blood cells (Kim et al. 2002), whereas arginase 2 is found in mitochondria of extrahepatic tissues, particularly in kidneys and brain (Cederbaum et al. 2004). The two arginases show a common ancestry and, interestingly, it was shown that the duplication of the parent gene occurred early in evolution, long before mammals and amphibians diverged (Morris et al. 1997).

Arginase 2 activity is induced in arginase 1 deficiency which may explain the fact that patients are less prone to hyperammonemia than patients with other UCDs (Spector et al. 1983; Grody et al. 1989, 1993; Cederbaum et al. 2004). The induction of arginase 2 may play a role in the pathogenesis of arginase 1 deficiency although this aspect has not yet been studied amply in patients or animal models.

Arginase 2 is thought to be relevant in states of increased collagen biosynthesis such as wound healing and tissue repairing but also in liver fibrosis, as it may direct ornithine to proline production due to its mitochondrial colocalisation with ornithine aminotransferase (OAT) (Fig. 1; Shearer et al. 1997). An arginase isoenzyme pattern similar to that in arginase 1 deficiency with a decreased activity of arginase 1 and an increased activity of arginase 2 has also been described for liver cirrhosis of other causes (Chrzanowska et al. 2009).

The different arginase isoforms have also been found to play an important role in macrophage activation and immune as well as inflammatory responses, and are thought to be involved in the pathophysiology of cardiovascular disease and metabolic disorders (Yang and Ming 2014).

However, the implications of the different arginase isoform functions on the pathogenesis of arginase 1 deficiency need further elucidation in the future studies.

Genetics

Arginase 1 deficiency is inherited as an autosomal-recessive trait. *ARG1*, the gene for liver arginase (arginase 1), is located on chromosome 6q23, encompassing a 15 kb region and comprising 8 exons (Sparkes et al. 1986). It was cloned in 1986 (Haraguchi et al. 1987).

Many different pathogenic mutations have been described (Uchino et al. 1995; Vockley et al. 1994, 1996; Hertecant et al. 2009; Carvalho et al. 2012a; Wu et al. 2013; Cohen et al. 2012; Baranello et al. 2014; Scaglia and

Lee 2006), including a complex re-arrangement (Mohseni et al. 2014) and whole-gene deletion (Korman et al. 2004). Hyperargininemia is most commonly caused by heterogeneous missense mutations in the occurring in highly conserved regions of the *ARG1* gene (Vockley et al. 1996) that disrupt the active sites required for the catalytic reaction or interfere with the assembly of the protein trimer (Ash et al. 1998).

Most patients have private mutations, although there are prevalent mutations in Portugal (Cardoso et al. 1999) and the French–Canadian population (Qureshi et al. 1983).

No clear genotype–phenotype correlation has been established (Scaglia and Lee 2006), but interestingly a correlation between responsiveness to dietary treatment and different types of molecular defects in the *ARG1* gene was demonstrated (Uchino et al. 1995).

Diagnosis

Accumulation of L-arginine in plasma and other body fluids is the biochemical hallmark of arginase 1 deficiency. L-Arginine levels in plasma can increase up to 15-fold, and levels of up to 1500–1600 µmol/l have been reported (Terheggen et al. 1975; Grody et al. 1993). In CSF, L-arginine (Terheggen et al. 1969, 1970a; Cederbaum et al. 1979), and glutamine may be markedly elevated (Cederbaum et al. 1979; Picker et al. 2003). Urinary L-arginine excretion is also markedly increased. As L-arginine competitively inhibits the tubular reabsorption of cysteine and the dibasic amino acids lysine and ornithine, the urinary amino acid pattern may be reminiscent of cystinuria (Terheggen et al. 1970a).

Increased urinary orotic acid excretion supports the diagnosis; however, this is not specific for arginase 1 deficiency as it may be found in other UCDs and in other conditions such as lysinuric protein intolerance, hyperornithinemia–hyperammonemia–homocitrullinuria syndrome, mitochondrial myopathies, or as a result of disturbances of pyrimidine synthesis as well (Steiner and Cederbaum 2001; Bachmann and Colombo 1980, 1982; Bonham et al. 1999; Brosnan and Brosnan 2007). A functional decrease in OTC activity as a result of low ornithine levels and subsequent shunting of accumulating carbamoyl phosphate to the pyrimidine biosynthetic pathway (Fig. 1) has been proposed to account for this finding (Naylor and Cederbaum 1981; Qureshi et al. 1981).

Blood urea levels are typically low-normal in patients with arginase deficiency, but generally not as low as in other patients with other UCDs and have been shown to rise with increased protein intake. This was already observed in the first patients (Terheggen et al. 1970b) and together with the reduced predisposition to hyperammonemia as compared with other UCDs soon led to the assumption that a second form of arginase existed (Cederbaum et al. 1979), which was later proven correct.

Diagnosis can be confirmed by determination of arginase activity in red blood cell extracts (Tomlinson and Westall 1964), as there is a good correlation between arginase activity in red blood cells and liver (Michels and Beaudet 1978; Cederbaum et al. 1979). White blood cell arginase activity may also be diagnostic (Cederbaum et al. 1979). Moreover, molecular genetic analysis of the *ARG1* gene is widely available (see "Genetics").

Arginase 1 deficiency is accessible to newborn screening by tandem mass spectrometry (Rashed et al. 1999; Chace et al. 2002) and is part of several newborn screening programs (Naylor 1982). However, patients might be missed when screening takes place too early, as L-arginine levels may not be markedly elevated in the first days of life (Terheggen et al. 1975), and at least one case that was missed by newborn screening has been reported (Crombez and Cederbaum 2005).

Arginase 1 is expressed in fetal erythrocytes at 16–20 weeks of gestation at levels comparable to the postnatal levels (Spector et al. 1980), and percutaneous umbilical blood sampling has been used for prenatal diagnosis (Snyderman et al. 1979; Hewson et al. 2003). If both pathogenic mutations are known in affected family members, prenatal diagnosis may also be performed by mutation analysis in chorionic villous tissue or in amniotic fluid cells.

Clinical characteristics

As arginase 1 deficiency is a rare condition, there are only single case reports and a few case series which describe a wide variability in the clinical presentation of patients, ranging from acute neonatal or early onset presentation with or without severe hyperammonemia to a hepatic phenotype and even a rare, adult onset of neurologic findings.

As opposed to other UCDs, only few cases with a neonatal manifestation of arginase 1 deficiency have been reported. Symptoms in the neonatal period include hepatomegaly, neonatal cholestasis, and liver failure but also drowsiness, seizures and cerebral edema with mild or moderate elevations of ammonia of up to 250 µmol/l (Jorda et al. 1986; Picker et al. 2003; Braga et al. 1997; Schiff et al. 2009). Interestingly, there are no reports of cases of severe hyperammonemia in the first days of life as typically seen in other urea cycle disorders.

Most patients are described as healthy in their first months or even years of life. Failure to thrive is often one of the first symptoms, and growth retardation or short stature is evident in many patients (Cederbaum et al. 1977;

Crombez and Cederbaum 2005; Carvalho et al. 2012b). Microcephaly has been reported in up to 40 % of patients (Prasad et al. 1997; Carvalho et al. 2012b).

Plasma ammonia levels are often normal or only mildly increased when patients are well. The majority of patients experience mild or moderate hyperammonemia. However, in contrast to other UCDs, severe hyperammonemic crises only rarely occur. Nevertheless, fatal hyperammonemic episodes have been reported (Grody et al. 1993; Prasad et al. 1997). Episodes of hyperammonemia precipitated by minor viral illness or without apparent trigger factors have been reported in adolescents or young adults (Zhang et al. 2012; Grody et al. 1993). The occurrence of severe hyperammonemic episodes during menstrual periods, which was eliminated by hormonal menses cessation or hysterectomy, has been reported for two female patients suggesting a relationship between ammonia metabolism and the menstrual cycle (Grody et al. 1994; Boles and Stone 2006). Patients may present with irritability, nausea, vomiting, or anorexia, probably representing intermittent or chronic hyperammonemia. Spontaneous avoidance of high-protein foods is frequently observed (Carvalho et al. 2012b).

Developmental delay and clumsiness usually develop during the first years of life. The most conspicuous clinical sign of arginase 1 deficiency is the development of progressive spastic paraplegia (predominantly on the lower extremities). Arginase 1 deficiency has occasionally been misdiagnosed as cerebral palsy (Scheuerle et al. 1993; Prasad et al. 1997), and a late presentation of acute-onset paraplegia at adult age has also been reported (Cowley et al. 1998). Furthermore, ataxia and dystonia have been observed in a few patients (Crombez and Cederbaum 2005; Scaglia and Lee 2006; De Deyn et al. 1997; Carvalho et al. 2012b).

Most patients show some degree of cognitive impairment, and both loss of developmental milestones and severe intellectual disability may occur (Crombez and Cederbaum 2005; Carvalho et al. 2012b; Prasad et al. 1997).

Seizures may be the presenting symptom in arginase I deficiency, and epilepsy and EEG abnormalities are common and for most part not related to hyperammonemic episodes (Terheggen et al. 1982). No specific abnormal EEG pattern has been described (Gropman et al. 2007). Epilepsia partialis continua and nonconvulsive status epilepticus have been reported in some patients with arginase 1 deficiency (Grioni et al. 2014).

Magnetic resonance imaging (MRI) studies have shown variable cerebral and less often cerebellar atrophy (Gungor et al. 2008; Carvalho et al. 2012b; Schiff et al. 2009), ischemic changes and edema, signal changes in the posterior putamina and insular cortex (Gungor et al. 2008), and abnormal myelination (Brockstedt et al. 1990). Similar findings are recognized in most other UCDs in which hyperammonemia is a pathophysiologic factor (Blaser and Feigenbaum 2004). Multicystic encephalomalacia was described in a patient in her 30 s who, despite treatment, had persistently high plasma arginine levels (Segawa et al. 2011).

Magnetic resonance spectroscopy (MRS) studies found an increased glutamate/glutamine peak in acute presentations in neonates and infants (Jain-Ghai et al. 2011; Picker et al. 2003) as it has been described in other UCDs (Choi and Yoo 2001; Kojic et al. 2005) and also in hepatic encephalopathy (Rovira et al. 2008). A single report of a single voxel peak at 3.8 ppm in two siblings with a classical infantile presentation assumed to represent arginine (Gungor et al. 2008) could not be reproduced in other patients with arginase 1 deficiency who showed no metabolic abnormalities at all on MRS (Carvalho et al. 2012b). Diffusion tensor imaging has been used to demonstrate corticospinal tract alterations (Oldham et al. 2010).

Arginase 1 deficiency may also present as neonatal cholestasis which may resolve on conservative treatment or progress to liver cirrhosis requiring liver transplantation (Martins et al. 2010; Braga et al. 1997; Jorda et al. 1987).

Hepatomegaly can be present, especially during hyperammonemic crises (Jorda et al. 1986; Braga et al. 1997; Edwards et al. 2009; Scaglia and Lee 2006). Mild hepatic dysfunction with transient elevation of liver transaminases and coagulation abnormalities during catabolic episodes has been observed in a few patients with an otherwise typical neurological picture, and cases of persistent coagulopathy have been reported (Scaglia and Lee 2006; Crombez and Cederbaum 2005; Brusilow 2001; Carvalho et al. 2012b). Furthermore, a patient with liver cirrhosis and hepatocellular carcinoma without any other risk factors has been reported (Tsang et al. 2012). Variable degrees of hepatic cirrhosis also occur in other UCDs (LaBrecque et al. 1979; Mori et al. 2002), and increased levels of L-arginine have been observed in patients with liver cirrhosis with progressive loss of renal function (Kayali et al. 2009).

Treatment and outcome

Only limited data are available on clinical follow-up of patients with arginase 1 deficiency, and most information on outcome is based on retrospective reports or on single assessments.

Management of arginase 1 deficiency aims to lower L-arginine levels and to prevent hyperammonemia. Treatment resembles that of other urea cycle disorders without the use of L-arginine or L-citrulline (Haberle et al. 2012). The dietary intake of arginine and protein has to be limited to reduce arginine plasma levels. However, a sufficient reduction of L-arginine levels can be very difficult

to achieve, particularly in patients with *ARG1* mutations that have severe effects (Uchino et al. 1995). L-Arginine levels below 200 µmol/l, which is a treatment goal, may only be achieved in milder cases. Dietary treatment of arginase 1 deficiency requires a particularly rigorous protein restriction (Cederbaum et al. 1982). As the natural protein tolerance is usually too low to meet requirements for cellular functioning and to achieve normal growth and metabolic stability, up to 50 % of the protein requirement has to be given in the form of essential amino acid supplements, more than usually required for other UCDs. As in other UCDs, sodium benzoate, sodium phenylbutyrate and sodium phenylacetate are additionally given to stimulate the excretion of nitrogen in the form of hippuric acid and phenylacetylglutamine, respectively (Qureshi et al. 1984; Batshaw et al. 2001) and to lower L-arginine formation.

It has been shown that dietary treatment may lower L-arginine levels to near normal levels in plasma as well as CSF in some patients (Cederbaum et al. 1982; Snyderman et al. 1979). Optimal treatment can achieve a favorable outcome and prevent further neurological deterioration. A few patients treated from birth were reported to remain largely asymptomatic until their 30 s (De Deyn et al. 1997; Snyderman et al. 1979; Crombez and Cederbaum 2005); however, in several patients including the three sisters reported herein, L-arginine levels may remain persistently elevated, and the neurological findings progress (Baranello et al. 2014). One patient was reported with a good neurodevelopmental outcome at age 6 years who was treated from age 3 months with a protein restriction which did not result in continuously lowering L-arginine levels below 268–763 µmol/L and sodium benzoate suggesting a potential benefit of early pharmacologic intervention (Edwards et al. 2009).

A previous literature review found a clinical improvement in 50 % of the patients and a stabilization in a further 25 % under treatment, whereas 25 % of patients experience a progression of their disease despite treatment (Prasad et al. 1997).

Spasticity may progress despite conservative treatment and may require injections of botulinum toxine or orthopaedic surgery.

As in other UCDs, valproic acid should be avoided as it may exacerbate hyperammonemia (Christmann et al. 1990).

Transfusion of whole blood or erythrocytes has been shown to improve plasma levels of L-arginine and ammonia for a period of up to about 3 months and also to a clinical improvement (Mizutani et al. 1987a; Jain-Ghai et al. 2011; Sakiyama et al. 1984), even though the first report of a trial of enzyme replacement therapy using erythrocyte transfusions showed discouraging results with no significant decrease of blood arginine or clinical improvement (Michels and Beaudet 1978). The positive effect is probably due to the presumed activity of arginase 1 in transfused red blood cells which is well studied in the context of post-transfusional immunosuppression (Bernard et al. 2007). However, this has not been discussed as a long-term treatment option for arginase 1 deficiency.

A therapeutic regimen analogous to GAMT deficiency with ornithine and creatine supplementation and sodium benzoate has been shown to decrease GAA levels and reduce the frequency of seizures in a patient with arginase 1 deficiency and severe epilepsy (Amayreh et al. 2014).

Liver transplantation cures the enzymatic deficiency in arginase 1 deficiency in the liver and allows termination of dietary and nitrogen scavenger treatment (Whitington et al. 1998). It has been shown to lead to a complete normalization of L-arginine, ammonia and guanidinic compound levels in plasma on an unrestricted diet and to prevent progressive neurological impairment, even though pre-existing neurological damage may not be reversed (Silva et al. 2001, 2013).

Conclusion and perspectives

Arginase 1 deficiency is one of the rarest UCDs and presents with a markedly different clinical picture compared to other UCDs. Severe hyperammonemia does not commonly occur. Patients typically develop distinct progressive neurological features such as seizures and spastic paraplegia in the first years of life. A hepatic phenotype with neonatal cholestasis and the development of liver cirrhosis may also occur.

Pathophysiological processes have not been fully understood yet, although accumulation of L-arginine or related compounds has been implicated to contribute to the development of the distinct neurological findings. The existence of a second isoform of arginase which is induced in arginase 1 deficiency may play a role in the pathogenesis of the disease and warrants further elucidation.

Treatment resembles that of other UCDs with a strict dietary protein restriction to reduce arginine levels and the use of nitrogen scavenging drugs. A deeper understanding of the pathophysiological mechanisms may allow more specific treatment options in the future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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