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REVIEW

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The role and control of arginine levels in arginase 1 deficiency

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Abstract

Arginase 1 Deficiency (ARG1-D) is a rare urea cycle disorder that results in persistent hyperargininemia and a distinct, progressive neurologic phenotype involving developmental delay, intellectual disability, and spasticity, predominantly affecting the lower limbs and leading to mobility impairment. Unlike the typical presentation of other urea cycle disorders, individuals with ARG1-D usually appear healthy at birth and hyperammonemia is comparatively less severe and less common. Clinical manifestations typically begin to develop in early childhood in association with high plasma arginine levels, with hyperargininemia (and not hyperammonemia) considered to be the primary driver of disease sequelae. Nearly five decades of clinical experience with ARG1-D and empirical studies in genetically manipulated models have generated a large body of evidence that, when considered in aggregate, implicates arginine directly in disease pathophysiology. Severe dietary protein restriction to minimize arginine intake and diversion of ammonia from the urea cycle are the mainstay of care. Although this approach does reduce plasma arginine and improve patients' cognitive and motor/mobility manifestations, it is inadequate to achieve and maintain sufficiently low arginine levels and prevent progression in the long term. This review presents a comprehensive discussion of the clinical and scientific literature, the effects and limitations of the current standard of care, and the authors' perspectives regarding the past, current, and future management of ARG1-D.

KEYWORDS

arginase deficiency, guanidino compounds, hyperargininemia, inborn error of metabolism, urea cycle disorder

Synopsis

ARG1-D is a distinct urea cycle disorder with a progressive neurologic phenotype. This review presents a comprehensive discussion of evidence from genetically manipulated mouse models and observations from clinical practice that implicate high arginine levels directly in disease pathophysiology.

1 | INTRODUCTION

Arginase 1 Deficiency (ARG1-D) is a rare, progressive inborn error of metabolism that results in persistent hyperargininemia and debilitating cognitive, neurologic, and mobility impairments.[1,2] These clinical impairments consistently manifest in patients with ARG1-D, although with varying age of onset and rate of progression.[2,3] Although ARG1-D shares some clinical characteristics with other urea cycle disorders (UCDs), there are several distinct biochemical and clinical features of ARG1-D that suggest a unique mechanism driving development and progression of disease manifestations. Neurotoxic effects of elevated levels of arginine and arginine metabolites, as well as a mechanistic role of chronic hyperargininemia in the development and progression of neurologic manifestations have long been proposed,[4–10] and are supported by both empirical studies and clinical evidence discussed here.

1.1 | Arginase 1 deficiency is a distinct urea cycle disorder

The urea cycle comprises six consecutive enzymatic reactions and two transporters in the liver that detoxify ammonia through conversion into urea, which is excreted through the kidneys. Under normal conditions, arginase 1 hydrolyzes arginine into ornithine and urea in the final step of the cycle. Mutations in the *ARG1* gene lead to impaired or absent arginase 1 activity and, as a direct effect of defective metabolism, intracellular hepatic arginine accumulates at levels approximately 50-fold higher than normal (Figure 1).[11] This excess arginine is released to the plasma and subsequently accumulates in other organs (including brain and cerebrospinal fluid [CSF]),[8,12] as a result of arginine being readily transported and maintained in an equilibrium between different tissues and plasma.[13–15] Elevated levels of arginine and arginine-derived guanidino compounds, putative neurotoxins generated through downstream enzymatic pathways external to the urea cycle,[8,11,12,16–18] are well-documented in the plasma/serum and CSF of patients with ARG1-D as well as rodent models of this multisystem disorder.[1,4,8]

Biochemically, markedly elevated plasma arginine is the most readily apparent feature of ARG1-D. Normal plasma arginine levels range from 40 to 115 μmol/L[19] but are typically >300 μmol/L in ARG1-D and often much higher[20]; levels >10-fold normal have been reported. In contrast, arginine levels are low in other UCDs because of upstream metabolic abnormalities that diminish endogenous arginine production—in fact, arginine supplementation is indicated for all UCDs other than ARG1-D.[20] In most UCDs, hyperammonemia is a common and potentially life-threatening complication. Hyperammonemic episodes, often severe, may occur throughout life and can cause encephalopathy, neurocognitive sequelae, or even death. Symptomatic hyperammonemia and hyperammonemic crisis are comparatively less common in ARG1-D, probably because upstream ammonia detoxification processes (through activity of

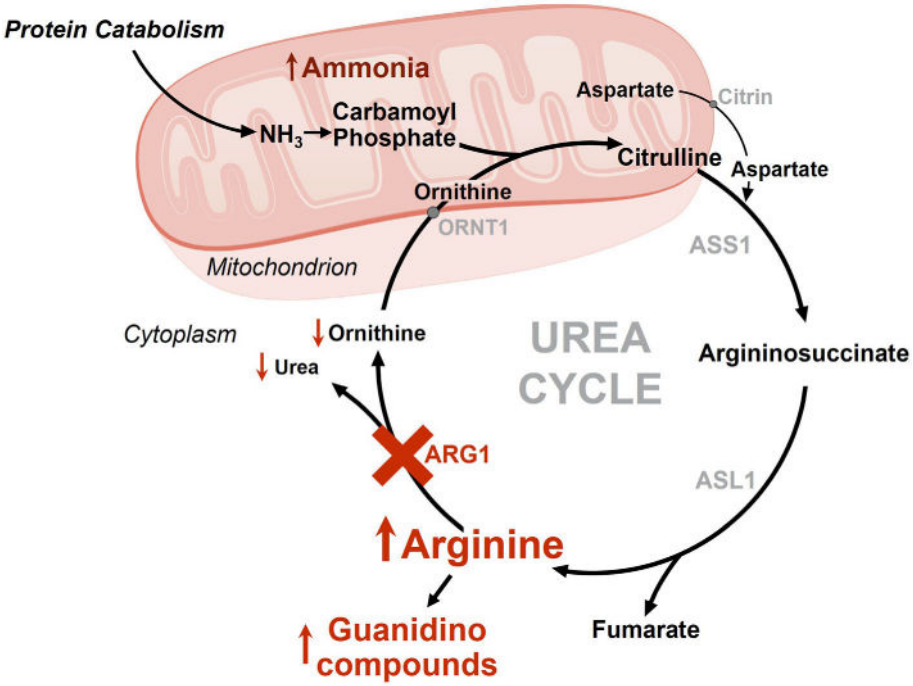

FIGURE 1 Urea Cycle Dysfunction in Arginase 1 Deficiency. Loss of arginase 1 enzymatic activity results in pathologic accumulation of arginine, decreased levels of its urea cycle products (ornithine and urea), and increased levels of guanidino compounds. ARG1, arginase 1; ASL1, argininosuccinate lyase; ASS1, argininosuccinate synthetase 1; ORNT1, ornithine transporter 1. Adapted with permission from Blair NF, Cremer PD, and Tchan MC. *Pract Neurol.* 2015;15:45–48. doi:10.1136/practneurol-2014-000916

enzymes preceding arginase 1 in the urea cycle) remain intact.[20,21]

The importance of hyperammonemia in most other UCDs is reflected in their management and clinical course, wherein early manifestations of the more complete enzyme deficiencies become apparent in the first days or weeks of life and commonly involve signs and symptoms driven by ammonia accumulation (e.g., cerebral edema, lethargy, anorexia, hypothermia, neurologic posturing, seizures, and coma). Cases of severe neonatal/infantile hyperammonemia in ARG1-D have been described but are uncommon.[22–26] Instead, the classic phenotype of ARG1-D involves insidious onset with manifestations developing typically in the first years of life and worsening progressively over time at variable rates; newborns typically appear healthy.[2,17,27–29] The clinical profile of ARG1-D includes seizures, developmental delay, and cognitive impairment as common manifestations. Unlike other UCDs, however, developmental delay and cognitive impairment in ARG1-D are progressive. Furthermore, spastic diplegia is a hallmark clinical feature of ARG1-D that differentiates this disorder from other UCDs, with its pathogenesis distinct from the known toxic effects of ammonia.[20,21,30] Patients with ARG1-D exhibit progressive spasticity that predominantly affects the lower limbs and worsens in severity and impact over time. As a result, these patients may initially stumble and appear clumsy, develop gait abnormalities and mobility impairments, and eventually lose the ability to walk independently.[17,29] Based on this clinical profile, ARG1-D is uniquely recognized among UCDs as a clinical mimic of cerebral palsy and hereditary spastic paraplegia.[31–34]

The pathophysiologic profile of ARG1-D strongly suggests that elevated arginine, rather than hyperammonemia, plays the key role in development and progression of manifestations.[2,4,28] Plasma arginine levels may be within or near the normal range in the immediate postnatal period, when infants appear phenotypically normal.[30] Furthermore, progression of manifestations with increasing duration of disease suggests a cumulative effect of persistently high arginine.[35,36] Clinical recognition of the importance of plasma arginine levels in ARG1-D is reflected in current management guidelines.[20] Treatment of other UCDs is focused on reducing risk of hyperammonemia and addressing acute hyperammonemic episodes,[20] but, as noted previously, hyperammonemia is less of a concern in ARG1-D. Preventing symptomatic hyperammonemia does not prevent progression or improve long-term outcomes in these patients. Instead, current guidelines for ARG1-D management focus on lowering plasma arginine, and specifically recommend maintaining plasma arginine levels at <200 μmol/L or as low as possible (aiming for the upper reference range).[20]

1.2 | Empirical studies implicate arginine in development and progression of ARG1-D manifestations

Multiple mouse models support a key role of arginine accumulation in ARG1-D pathophysiology. These animals demonstrate markedly elevated plasma arginine and guanidino compounds that lead to phenotypic abnormalities consistent with disease manifestations observed in patients with ARG1-D, including failure to thrive, seizures, spasticity, gait abnormalities, and mobility impairment.[37–42]

The most extensively characterized *Arg1* knockout model, first described by Iyer et al., was developed through replacement of *Arg1* exon 4 (the active site) with a neomycin resistance gene by homologous recombination that results in a total lack of liver arginase 1.[37] These mice are phenotypically indistinguishable from wild-type littermates at birth and appear to behave normally for the first 10–12 days of life. Onset of hyperargininemia and hyperammonemia is followed by weight loss, central nervous system dysfunction (which manifests as gait instability, tremor, ataxia, lethargy, decerebrate posture, and seizure-like activity), encephalopathy, liver pathology, metabolic crisis, and death. Plasma arginine levels are approximately four-fold greater in these animals than wild-type comparators and rise to >10-fold normal levels during metabolic crisis. As expected, hyperargininemia is accompanied by marked increases in guanidino compounds in the serum as well as in the brain.[39,41,42] These mice ultimately succumb to severe hyperammonemia at approximately 14–21 days of life. The biochemical and phenotypic abnormalities stemming from arginine accumulation in these mice have been recapitulated in 2 different conditional adult-onset knockout mouse models generated using tamoxifen-inducible Cre-Lox mice with floxing of *Arg1* exons 7 and 8.[40,43] As is characteristic of the exon 4–targeted *Arg1* knockouts, the adult-onset models demonstrate hyperargininemia upon tamoxifen induction and ensuing signs of physical, neuromotor, and behavioral abnormalities such as growth disparity, weight loss, hunched body posture, difficulty standing, gait abnormalities (e.g., instability, staggering, irregular steps, and shortened stride length), and progressive ataxia.[40,43] Also like the exon 4–targeted knockouts, both inducible models follow a rapid course of metabolic disruption, including increased arginine, guanidino compounds, and ammonia, among other perturbations, as well as lethal hyperammonemia within 2–3 weeks.[40,43] A consistent observation across all three models is that hyperargininemia is established by the time that phenotypic abnormalities become apparent, suggesting that the phenotype may be biochemically driven by accumulation of arginine and arginine metabolites resulting from

hepatic *Arg1* disruption.[37,40,43] This hypothesis is further supported by a recent characterization of another genetic mouse model that lacks expression of *Arg1* in neural cells only.[44] Although small decreases were noted in the volume of two brain structures involved in motor activity of these neural-specific knockouts, others were unchanged and their gait was largely unaltered compared with wild-type controls. Assessment of blood amino acids revealed that arginine levels were also unchanged in mice lacking neural expression of *Arg1*. The striking contrast between this genetically manipulated model and the global or liver-specific *Arg1* knockouts led the authors to two important conclusions: (1) that hyperargininemia and neurologic manifestations of ARG1-D are driven by the toxic metabolic environment that results from loss of hepatic arginase 1, and (2) that reducing arginine levels in the blood represents the best chance to avoid neurologic manifestations.[44]

Restoration of *Arg1* in transgenic mouse models of ARG1-D has provided further evidence of a key role of arginine in disease manifestations, as pioneered by Gerald Lipshutz's group at UCLA. In an early proof-of-concept study, the exon 4–targeted *Arg1* knockout mice[37] were treated with *Arg1* gene transfer delivered using an adeno-associated viral (AAV) vector administered on the second day of life.[38] Whereas all untreated knockouts died within 24 days, AAV-treated mice (i.e., those with hepatic arginase 1 restored) demonstrated normal plasma arginine levels, less-severe hyperammonemia, improved weight gain, and prolonged survival with 89% alive through >8 months. Results of a detailed characterization of the biochemical, neuromotor, and neurobehavioral phenotype of knockout mice with AAV-mediated restoration of *Arg1* also supports this hypothesis.[39] Brain development at 4 months was similar between treated knockouts and wild-type littermates, with no abnormalities or lesions evident in key brain structures such as olfactory bulbs, cerebral cortex, basal ganglia, hippocampus, thalamus, cerebellum, or pons. A battery of functional assessments revealed no differences in exploratory activity, cerebellar function, spatial learning, or behavioral responses, or in body posture, tremor, locomotor activity, gait, grip strength, or righting reflexes. Notably, normal brain development and neurologic phenotype were observed in the context of reversal of metabolic abnormalities. By 3 weeks after AAV-mediated gene transfer, brain and serum levels of arginine were normalized or below control levels. Furthermore, serum guanidino compounds, which were markedly elevated in untreated knockout mice, were decreased to near-normal levels in sera and brain tissue of treated knockouts.[39]

The prominent, progressive spasticity observed in patients with ARG1-D and the analogous neuromotor abnormalities observed in *Arg1*-deficient mice prompted further investigations of the motor cortex in untreated knockout mice and knockouts with AAV-mediated *Arg1* hepatic gene therapy.[41,45] Altered circuitry in the motor cortex was observed in untreated knockouts at postnatal day 15 (after development of hyperargininemia) with decreased dendritic arborization, decreased numbers of excitatory and inhibitory synapses, and abnormal synaptic transmission, suggesting a potential arginine-driven neural mechanism of motor dysfunction in ARG1-D.[45] Neuronal structure and cortical circuitry were virtually normal in knockout mice with neonatal *Arg1* restoration.[45] In a second study, microarray expression analysis in untreated *Arg1* knockouts suggested abnormalities in myelinating oligodendrocytes that were supported by evidence of marked subcortical dysmyelination in key motor structures including the corpus callosum and caudate putamen.[41] Compared with wild-type mice, the *Arg1*-deficient mice had fewer myelinated axons in the motor cortex, pyramidal tract, and corticospinal tract, as well as decreased thickness of the myelin sheath where myelination was evident; axonal degeneration and decreased dendritic complexity were also observed. Among the knockouts receiving AAV treatment at postnatal day 2, myelinated axon density, oligodendrocyte wrapping of axons, and axonal integrity were largely normal, indicating prevention of neural abnormalities through restoration of functional arginase 1 and normalization of plasma arginine.[41] The results of these studies implicate arginine levels, rather than residual or induced brain arginase 1 or 2. Wild-type mice express only low levels of arginase 1 and arginase 2 confined to specific brain areas. Furthermore, there is little to no increase in brain arginase 2 in *Arg1* knockout animals, and little to no increase in brain arginase 1 in genetically corrected *Arg1* knockouts. Finally, in a more recent mouse model also spearheaded by the Lipshutz group, a lipid nanoparticle carrying human *Arg1* mRNA was administered intermittently to constitutive *Arg1* knockout mice to restore their hepatic arginase 1 activity.[46] Normalization of plasma arginine and reductions in guanidino compounds were achieved in the mice receiving lipid nanoparticle/*Arg1* mRNA compared with untreated knockouts and wild-type controls; these biochemical changes were associated with a dramatic recovery of myelin density, increased myelin sheath thickness, and normal growth and survival.[46]

This evidence of abnormal neurophysiology and dysmyelination is consistent with the limited available observations reported in children with ARG1-D. In one patient with toe walking and spastic paraplegia, among other signs of pyramidal tract dysfunction affecting his lower limbs, neurophysiologic assessment revealed prolonged latency of motor evoked potentials, indicating

involvement of the corticospinal tract.[47] In another case, a patient exhibited the characteristic ARG1-D clinical profile and trajectory, with an uneventful infancy before insidious onset of progressive neurologic deterioration.[48] At 2.5 years of age, spastic diplegia and permanent loss of speech were evident, followed by loss of locomotion over the course of several months, and ultimately spastic tetraplegia and reliance on a wheelchair at only 3 years and 10 months of age. Plasma ammonia was only slightly elevated above normal levels, whereas arginine levels were nine-fold higher than normal in the plasma and 2.5-fold higher than normal in the CSF. Electroencephalography (EEG) showed multifocal discharges with abnormal background activity and absence of short latency responses in brainstem evoked potentials. Magnetic resonance imaging revealed dysmyelination as well as an undersized cerebellum, enlarged cerebral ventricles, and thinning of the corpus callosum. At 9 months after diagnosis of ARG1-D and initiation of dietary restriction, background activity on EEG was normalized and short latency responses were improved in parallel with lowering of arginine levels. Increased severity of protein restriction produced further reductions in arginine that were accompanied by additional improvement or normalization of brainstem evoked potentials. Importantly, objective improvement of neurologic function was reflected through improvements in alertness and motor activity.[48] Lastly, a patient evaluated in a study conducted with the Urea Cycle Disorders Consortium (UCDC) was also found to have corticospinal tract abnormalities consistent with his neuromotor deficits.[49] This patient exhibited characteristics not uncommon in ARG1-D in the early postnatal period, including poor feeding, vomiting, and poor growth; however, developmental milestones were normal. Before diagnosis at 4 years of age, he demonstrated increasing fall frequency and decreasing motor skills followed by development of significant lower-limb spasticity and seizures. At diagnosis, plasma arginine was predictably elevated and treatment with dietary restriction and ammonia diversion was initiated. At 16 years of age, his cognitive performance with regard to visual memory and language was normal and he was succeeding scholastically, but impairments in complex problem-solving and organization were evident in addition to impaired motor strength. At 17 years, he was ambulatory without orthotics or assistive devices but had increased tone, hyperreflexia, and clonus in the lower extremities consistent with the spasticity that manifested in his early childhood. Diffusion tensor magnetic resonance imaging revealed altered integrity and microstructural damage in the white matter of regions involved in motor function—specifically, the central pons extending into the cerebellum at the level of corticospinal tract crossing as well as adjacent to the corpus callosum. There was also a significant reduction in corticospinal tract fiber count compared with matched control subjects, further indicating neuronal damage to motor circuitry in ARG1-D.[49] Abnormalities in neuromotor circuitry and corticospinal tract damage in particular have not been reported in patients with more proximal UCDs and were not observed in patients with ornithine transcarbamylase deficiency ($n = 23$) in the UCDC diffusion tensor imaging study, which further implicates arginine in the pathology of ARG1-D.[49]

We believe that these neurologic abnormalities reflect the neurotoxic effects of arginine and/or the guanidino compounds that accumulate in conjunction with, and as a result of, arginine elevation.[8,11,12,17] Guanidino compounds, both as a class and individually, have neurotoxic effects on the brain and on brain cells in culture.[16,18] For example, guanidino compounds that are increased in ARG1-D, such as guanidinoacetic acid and guanidinovaleric acid, have been empirically shown to induce epileptiform and convulsive activity in rodents.[18] Likewise, argininic acid and guanidinovaleric acid, at levels comparable to those observed in ARG1-D, alter evoked depolarizing responses in cultured spinal cord neurons.[50] Although this neurotoxicity has been demonstrated independent of the effects of arginine, guanidino compounds (and their effects) in ARG1-D are inextricably linked with elevation of arginine, the proximal substrate.[42] It has also been suggested that ornithine deficiency, which is observed in pyrroline-5-carboxylate synthetase deficiency (P5CSD), or distorted arginine/ornithine imbalance, which occurs in hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, may play a role in the spasticity sometimes observed in these two disorders.[34,51–53] However, ornithine deficiency is not an established feature of ARG1-D, and both P5CSD and HHH syndrome differ from ARG1-D in that spasticity occurs with variable prevalence and late onset, in contrast with the regular and relentless occurrence of spasticity in ARG1-D. As such, they would not support ornithine deficiency as an important pathogenic contributor in ARG1-D. Lastly, downstream effects of excessive arginine on nitric oxide and promotion of oxidative stress and excitotoxicity have also been hypothesized.[28,49]

1.3 | Clinical evidence implicates arginine in development and progression of ARG1-D manifestations

With an estimated global prevalence of only 1:726000,[54] the rarity of ARG1-D poses a challenge to characterizing the pathophysiology and mechanisms driving progression

in humans. Most clinical evidence to date is largely anecdotal and based on individual cases, familial series, or retrospective case analyses. Nonetheless, the clinical evidence is consistent with empirical evidence from mechanistic studies in mouse models.

The first ARG1-D patients described in the literature were three female siblings, the older two of whom developed seizures, psychomotor delays, and spasticity within the first years of life.[55–57] At presentation and biochemical evaluation for the two older sisters (ages 5 years and 1.5 years), significantly diminished/near-undetectable arginase one enzymatic activity and markedly increased arginine levels in serum and CSF were evident; only mild hyperammonemia was observed. Because of this family history, a third sister was assessed at birth and was found to also have ARG1-D.[57] Despite early initiation of treatment with a low-protein diet at 8 weeks of age, her plasma arginine remained significantly elevated at ~800 μmol/L and onset of motor abnormalities was evident by age 5 months. She experienced a progressive clinical course similar to her siblings, with psychomotor delays and lower-limb spasticity evident by 3 years of age.[57]

Over the ensuing five decades since these first patients were described, a clear clinical and pathophysiologic profile of ARG1-D been borne out with striking consistency through numerous reports: deleterious effects of high arginine and/or dysregulation of arginine metabolites become evident typically in the first years of life and increase in severity and extent throughout the patient journey.[2–4,7,9,28,30,32,34,47,58–65] Elevated plasma arginine, whether as the primary driver or proximal causal component of downstream toxicity, is associated with progressive intellectual disability, global developmental delay, seizures, and uniquely, with progressive spasticity. Of note, seizures in ARG1-D patients are not attributed exclusively to hyperammonemic events.[8,12] The neurotoxic effects of guanidino compounds, which increase in the plasma and CSF as a result of elevated plasma arginine, contribute to seizure susceptibility.[16–18] The morbidity associated with ARG1-D puts these patients at risk for early mortality.[30] The specific factors driving early mortality in ARG1-D are not yet clear; precipitating events reported in the literature are diverse and the end stages of disease remain to be more fully characterized.

A detailed clinical characterization of the relationship between biochemistry and functional outcomes in multiple UCDs, performed by the UCDC, more directly implicates chronic high arginine as the driver of development and progression of ARG1-D manifestations.[36] Patients with ARG1-D were at greater risk than those with other UCDs for low IQ and poor performance in all neuropsychologic domains assessed. Consistent with the known biochemical profiles of ARG1-D and other UCDs, mean lifetime plasma ammonia was lower in the ARG1-D cohort compared with other UCDs (mean, 78.87 μmol/L vs. 127.22–139.59 μmol/L) and hyperammonemic episodes were less common. Elevated arginine (several fold normal in the ARG1-D cohort) was more tightly associated with poorer functioning in global and memory domains than any other biochemical marker evaluated, and higher plasma arginine levels were significantly correlated with poorer motor composite scores. Lastly, increasing cumulative arginine exposure (in terms of longer duration of disease) was an indicator of worse neuropsychiatric outcome among patients with ARG1-D. Individual case reports of patients with long-term follow-up have also documented phenomena strongly suggestive of arginine toxicity in ARG1-D. Periods of worsening hyperargininemia, whether because of poor treatment adherence or other factors such as biologic stressors, were accompanied by worsening of cognitive and mobility impairments that returned to patients' functional baseline upon re-establishment of their typical plasma arginine levels.[59,65–67]

In the first reports of ARG1-D treatment, dietary protein restriction was able to control hyperammonemia but not plasma arginine (which was lowered from pretreatment levels but remained elevated), and achieved only limited clinical improvement.[10,55–57] An important outcome of this early work was the exclusion of ammonia and the implication of arginine as a direct driver of disease pathophysiology; additionally, these reports established the challenge of lowering arginine levels in patients with ARG1-D. In subsequent reports, rigorous management with chemically defined amino acid diets was more effective, lowering plasma arginine and achieving clinical stability or improvement even in patients with advanced/severe disease (Table 1).[9,48,59,61] In adolescent/teenage siblings with established neurocognitive and neuromotor manifestations of ARG1-D, lowering of plasma arginine with a chemically defined diet resulted in clinical improvement.[9,61] Specifically, spasticity was lessened and mobility improved, independent feeding and toilet training were regained, and language improved.[61] Initiation of treatment in younger patients has been described to yield more meaningful clinical benefits.[58,63] In a patient with overt cognitive impairment, lower-limb spasticity, and toe walking, treatment was initiated upon diagnosis at age 7 years.[63] Limitation of natural protein lowered her plasma arginine by approximately 50%, from 8-fold to 4-fold normal levels. Further restriction with a second dietary formulation was able to reduce plasma arginine to near the upper limit of

TABLE 1 Clinical Evidence Supporting the Effectiveness of Arginine Reduction* for Improving Outcomes in ARG1-D

	Pre-treatment History of Manifestations	Plasma Arginine[a]	Clinical Outcomes
Case report			
Cederbaum[9] Cederbaum[61]	• 6 years: severe spasticity, hyperreflexia • 15 years: progressive physical and intellectual deterioration (severe psychomotor impairment with no speech or language comprehension, no interaction with environment, severe spasticity with difficulty moving, decreased gag reflex, poorly coordinated swallowing)	• Pretreatment: 7-fold ULN • Initial restricted diet: 5- to 6-fold ULN • Stricter diet: 2-fold ULN	• Regained ability to dress, feed self, brush teeth, use toilet independently • Improved language and regained capacity to respond to simple commands • Diminished spasticity and improved mobility
Cederbaum[9] Cederbaum[61]	• 2.5 years: clumsiness, hyperreflexia, ankle clonus, spasticity (predominantly affecting lower limbs) • 8 years: wheelchair-dependent, severe psychomotor impairment with no speech and minimal language comprehension, no bladder/bowel control, tiptoe gait, reduced gag reflex, poorly coordinated swallowing	• Pretreatment: 5-fold ULN • Initial restricted diet: 4-fold ULN • Stricter diet: near-normal	• Regained ability to speak and construct phrases/sentences • Regained bowel/bladder control • Regained ability to feed self, brush teeth independently • Improved concentration • Improved spasticity and mobility
Brockstedt[48]	• 2.5 years: spastic diplegia, loss of speech, worsening of mobility impairment • 3 years 10 months (diagnosis): intellectual disability, no intelligible speech, spastic tetraplegia (predominantly affecting lower limbs), wheelchair-bound, no reproducible short latency response in brainstem acoustic evoked potentials	• Pretreatment: 907 μmol/L (9-fold ULN) • Initial restricted diet: 4-fold ULN • Stricter diet: 2- to 3-fold ULN	• Improved alertness and motor activity • Improved/normalized brainstem evoked potentials
Lambert[63]	• 5 years: motor and cognitive impairment • 6 years 1 month: lower-limb spasticity, hyperreflexia, tiptoe gait, • 6 years 11 months (diagnosis): spasticity, tiptoe gait, hyperactivity • 7 years 7 months: progressive worsening of motor deficits	• Pretreatment: 895 μmol/L (10.5-fold ULN) • Initial restricted diet: 6-fold ULN • Stricter diet: 1.7-fold ULN	• Progressive improvement of muscle strength, mental skills, and mobility • Patient a community ambulator; able to run, ride bike, climb stairs
Snyderman[58]	• 3 months: vomiting, lethargy, tremor • 5 months: seizures, hyperreflexia, bilateral ankle clonus • 20 months: seizure recurrence, ataxia • 4 years (diagnosis): intellectual disability, tiptoe gait, ataxia, hyperactivity	• Pretreatment: 9.4 mg/dL (6-fold ULN) • Initial restricted diet ineffective • Stricter diet: 2- to 3-fold ULN	• Reduced hyperactivity • Improved ataxia and coordination • Improved mental capacity

(Continues)

TABLE 1 (Continued)

	Pre-treatment History of Manifestations	Plasma Arginine[a]	Clinical Outcomes
Snyderman[5]	• 2.5 years: vomiting, lethargy, hyperreflexia • 3 years 7 months (diagnosis): intellectual disability, developmental delay, hyperactivity, tiptoe gait, lower-limb spasticity	• Pretreatment: 9.95 mg/dL (7-fold ULN) • Initial restricted diet: 4-fold ULN • Stricter diet: 2- to 3-fold ULN	• Reduced hyperactivity • Improved ataxia and coordination • Improved mental capacity
Snyderman[59]	• Patient identified at and treated from birth (pre-symptomatic)	• Until 4 months of age: normal • Beyond 4 months: 2- to 3-fold ULN	• Physiologically, neurologically, and mentally normal • Average developmental assessments, through 2.5 years
Observational study			
Huemer[28]	• Three patients identified at and treated from birth (pre-symptomatic)	• Pretreatment: not applicable • Last follow-up at age 1–3 years: 256–574 μmol/L (ULN not available)	• Last follow-up at age 1–3 years: asymptomatic course in all three patients

Abbreviation: ULN, upper limit of normal.

[a]ULN reflects normal range or control range as defined in each case report.

*Arginine-lowering intervention comprised dietary protein restriction with essential amino acid supplementation for all patients.

normal, which was accompanied by substantial lowering of guanidino compounds. Over 2.5 years of treatment, the patient's cognitive function improved, spasticity was markedly decreased, and muscle strength improved; the patient was ultimately able to run, climb stairs without support, and ride a bicycle, and was a community ambulator.[63] Treatment from birth has actually been shown to delay or reduce progression, with some patients showing no overt manifestations of ARG1-D through 5 years of age (Table 1).[28,59] For example, in a 2016 case series, three patients ascertained through newborn screening and treated from infancy remained clinically asymptomatic through toddlerhood, the age of most recent follow-up.[28]

Additional clinical evidence supporting the relationship between plasma arginine levels and clinical outcomes comes from a 1984 case report of a boy with ARG1-D who lost his ability to stand, sit, or crawl by himself at the age of 3 years and was also experiencing rigidness in his legs and spastic quadriplegia. At the age of 5 years, an experimental therapeutic approach involving transfusion of healthy red blood cells (i.e., with functional arginase) was used to lower plasma arginine.[23,68] This approach, though not without limitations precluding clinical adoption, markedly decreased arginine levels in the serum and, as a result, in the CSF and resulted in clear clinical improvements, such that the boy became able to sit and roll by himself and manifested reduced spasticity.[68]

1.4 | Current management is insufficient to maintain adequately low arginine and does not prevent ARG1-D progression in the long term

Dietary protein restriction to lower plasma arginine levels is the mainstay of management for all UCDs, with particularly extreme protein restriction required in ARG1-D.[20] The flux of arginine into plasma depends on three key sources (dietary arginine intake, de novo arginine synthesis via the intestinal-renal axis, and whole-body intracellular protein turnover), of which the endogenous flux from protein turnover is the major contributor in humans.[15] Dietary restriction in ARG1-D is focused on limiting exogenous supply of arginine, but cannot address the endogenous production[15]; even during periods of good adherence to a restrictive diet, elevated arginine levels can persist.[3] As in all UCDs, ammonia is a product of the catabolism of every amino acid and the flux through the cycle is far greater than the flux for the catabolism of other individual carbon skeletons. Patients with ARG1-D may receive nitrogen scavengers as part of their management[20] to address ammonia levels but also to lower arginine levels based on a potential downstream effect of offloading nitrogen from the urea cycle. The combination of dietary protein restriction and ammonia diversion therapy can stabilize the ammonia levels in all UCDs in non-catabolic situations but is insufficient to lower plasma arginine levels to anywhere near the

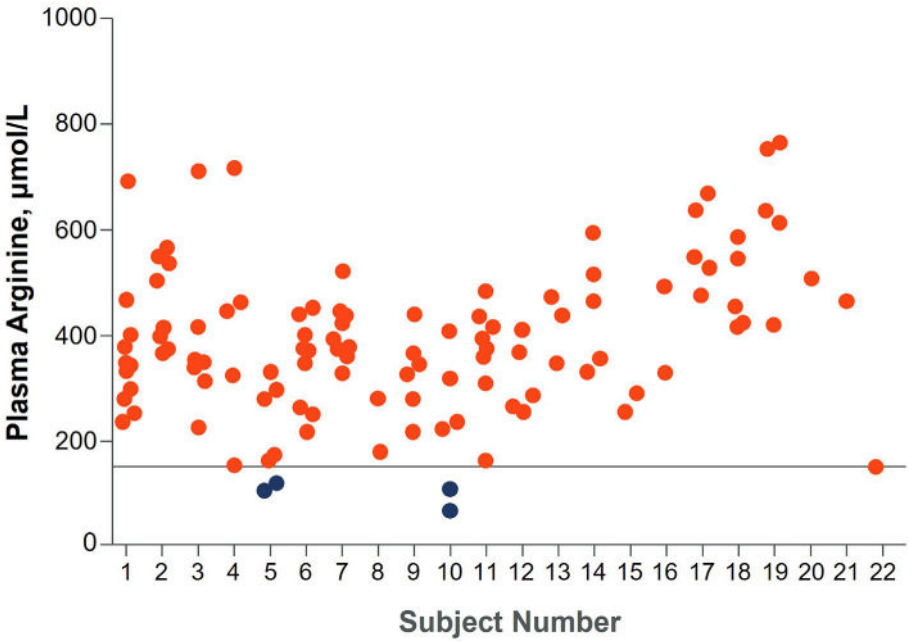

FIGURE 2 Plasma Arginine Levels With Current Standard of Care. Analysis of data from patients ($n = 22$) with Arginase 1 Deficiency in the Urea Cycle Disorder Consortium database. Dashed line indicates upper limit of normal applied to the study's laboratory assessments; current guidelines recommend maintaining plasma arginine <200 µmol/L. Blue dots represent arginine levels below the applied upper limit of normal of 150 µmol/L. Adapted with permission from Burrage LC, Sun Q, Elsea SH, et al. *Hum Mol Genet*. 2015;24 (22):6417–6427. doi:10.1093/hmg/ddv352

normal range in ARG1-D.[60] Nonetheless, as is evident throughout the literature and based on our clinical experience, even suboptimal reduction of plasma arginine can halt or delay progression and even improve patient outcomes, demonstrating the importance of effective arginine-lowering management approaches.

With currently available approaches, achieving and maintaining adequate reduction of plasma arginine in the long term is extremely difficult; thus, the guideline-recommended level of <200 µmol/L[20] is rarely achieved. As a result, most patients deteriorate over time and poor long-term outcomes are the norm.[2,6,28,65] In an analysis of published case reports of patients with ARG1-D, the median plasma arginine level (reported at any time in the patient journey, $n = 112$ patients) was 572 µmol/L; levels under treatment with dietary protein restriction ($n = 33$ patients) were also markedly elevated at a median of 400 µmol/L.[30] Even with a relatively young median age of 11 years in these patients, significant disease progression was evident, with lower-limb spasticity and intellectual disability reported in 84% and 82%, respectively.[30] Similarly, analysis of UCDC plasma arginine data from patients receiving standard of care management (22 patients; 1–13 measurements per patient) revealed that nearly all samples evaluated (97%) were above 150 µmol/L (value used as the upper limit of normal) and very few were <200 µmol/L; no patient had levels in the normal range in all samples/timepoints assessed **(**Figure 2**)**.[60] Median age at the most recent visit was 14.75 years; diagnosis was made at a median age of 3.25 years. Despite standard of care management in this cohort and the relatively young age at diagnosis/treatment initiation and follow-up, 89% of patients had developmental delay or intellectual disability; abnormal reflexes and abnormal tone were evident in 53% and 63% of patients, respectively, and 60% were nonambulatory.[60]

2 | SUMMARY

Collectively, the scientific literature demonstrates a key mechanistic role of elevated arginine as the proximal or direct driver of disease in ARG1-D. The ARG1-D biochemical profile and clinical manifestations are distinct from most other UCDs in which hyperammonemia is the primary concern. Persistent high plasma arginine in ARG1-D is accompanied by consistently and progressively manifesting debilitating neurologic and functional impairments, whereas reducing plasma arginine improves manifestations even in patients with established disease. Since tissue and CSF levels of arginine are in equilibrium with those of plasma, lowering plasma arginine to guideline-recommended levels is an important therapeutic approach, and is supported by improvements in neurologic and functional manifestations occurring with modulation of plasma arginine levels in ARG1-D demonstrated both in animal models and clinically. Furthermore, worsening severity of disease manifestations during acute decompensation events indicate toxic effects of spikes in arginine levels. Even when lowering of arginine is suboptimal, intervention with current management approaches has been shown to delay development of manifestations and to reverse many aspects of established cognitive and mobility impairment at both

the neurophysiologic and functional levels. However, the aggregate data from the UCDC highlight the difficulty in maintaining adequately low arginine levels with the current standard of care, even at highly specialized centers and with rigorous individualized disease management strategies; long-term outcomes remain poor with many patients developing significant disability over time. There is an urgent need for effective treatments that maintain long-term reduction, or even normalization, of plasma arginine levels in patients with ARG1-D to address the underlying mechanism of disease, thereby preventing progression and improving outcomes.

3 | PERSPECTIVE

As we seek better outcomes in ARG1-D, improvements in newborn screening algorithms for ARG1-D will allow diagnosis to be made with high sensitivity and specificity.[35,69] Whereas standard of care can maintain arginine levels in an acceptable therapeutic range for the first months or years of life, we have seen how difficult this can be in the longer term. Enzyme therapy has been shown to lower plasma arginine levels to the therapeutic range and to substantially reduce guanidino compounds; these biochemical changes are accompanied by meaningful improvements in mobility.[70–72] This potential therapy currently awaits FDA approval and represents the first step in advancing treatment of ARG1-D, which has been awaiting a therapeutic breakthrough for 40 years. Both gene and mRNA therapies have been validated in animal models[39,73] and must be demonstrated to be effective and safe in humans before they can be considered part of this more hopeful future of ARG1-D treatment. One of the authors (SDC) has been investigating ARG1-D for nearly 50 years and has been hoping for these promising therapeutic breakthroughs.

AUTHOR CONTRIBUTIONS

George A. Diaz: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.
Mark Bechter: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.
Stephen D. Cederbaum: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.

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ETHICS STATEMENT

All authors were compliant and followed the ethical guidelines, according to the requirements of JIMD.

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CONFLICT OF INTEREST

Dr Diaz has served as an advisor and clinical trial investigator for Aeglea. Dr Cederbaum has served as a consultant and/or advisor for several biopharmaceutical companies, including Aeglea. Dr Bechter is an Aeglea employee (Medical Affairs). No author received compensation for their role in writing this article.

DATA AVAILABILITY STATEMENT

There is no data associated with this manuscript.

INFORMED CONSENT/ANIMAL RIGHTS

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

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