Delays in Diagnosis are Associated With Poor Clinical Outcomes in Patients With Arginase 1 Deficiency

George A Diaz[1], Nicola Longo[2], Gillian Bubb[3], Susan L Potts[3], Mark W Bechter[3], James E Wooldridge[3], J. Lawrence Merritt II[4]

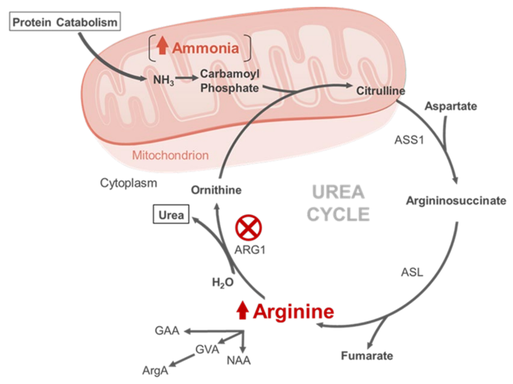
[1]Icahn School of Medicine at Mt. Sinai, New York, NY, USA, [2]University of Utah, Salt Lake City, UT, USA, [3]Aeglea BioTherapeutics, Austin, TX, USA, [4]University of Washington, Seattle, WA, USA

BACKGROUND

Disease Background and Current Management

- Arginase 1 Deficiency (ARG1-D) is a serious, progressive disease with early mortality and high unmet medical need due to an autosomal recessive disorder of arginine metabolism (**Figure 1**)[1]
- Clinical presentation is typically in childhood, with spasticity, intellectual disability, and/or seizures[2]
- Progressive spasticity is a key disease manifestation that is not commonly present in other urea cycle disorders[3]
- High levels of arginine and arginine-related metabolites are thought to cause the neurologic manifestations of ARG1-D[4]

Figure 1. The Urea Cycle



ASL = argininosuccinate lyase; ASS1 = argininosuccinate synthase 1; ARG1 = arginase 1. Arginine-derived metabolites: ArgA = R,S-argininic acid; GAA = guanidinoacetic acid; GVA = α-keto-δ-guanidinovaleric acid; NAA = Nα-acetyl-L-arginine.

- Episodic hyperammonaemia occurs in some patients[5,6]
- Current disease management approaches utilising severe protein restriction, essential amino acid supplementation, and ammonia scavengers have a limited impact on both plasma arginine levels and disease manifestations, with continued disease progression[3]

ARG1-D Diagnosis

- Diagnosis is confirmed by plasma amino acid testing that includes measurement of plasma arginine; Lack of disease awareness combined with the variably in presentation has led to notable delays in diagnosis and associated disease progression[7]
- ARG1-D can be misdiagnosed as other neurologic conditions, commonly cerebral palsy and hereditary spastic paraplegia[8-10]
- A mean delay of 4.3 years (range 0–20 years) before diagnosis has been reported in the literature[7]

OBJECTIVE

- This literature review was performed to collate available published data to: 1) better define the clinical presentation of patients with ARG1-D; 2) review disease management approaches; 3) provide insights on the age and causes of early mortality

METHODS

- A PubMed search was undertaken of unique case reports of patients with ARG1-D published in the English language between 1965 and 2018, followed by review of relevant data.
- Cases were defined as unique based on assessment of country of origin, sex, age at diagnosis, age at presentation, and age at symptom onset

RESULTS

- The initial search identified 140 case reports of patients with ARG1-D.
- Patients had markedly elevated plasma arginine, and arginine-derived metabolites when measured **(Table 1)**

Table 1. Baseline demographics and characteristics of reviewed unique cases

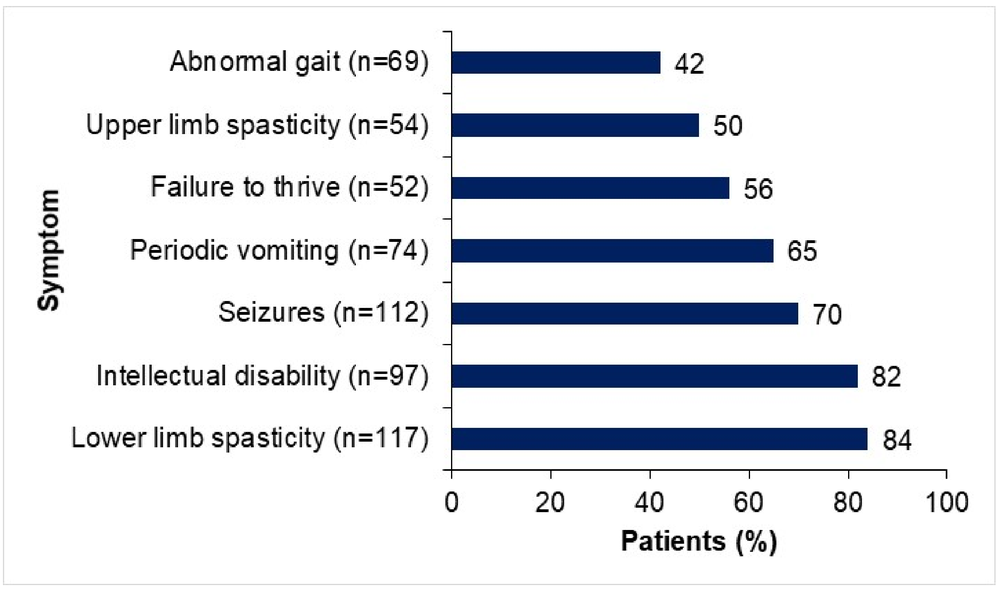
	n	Median (Q1–Q3)[a]
Age at time of study	103	11 (<1–39)
Sex, males, n (%)	125	73 (58)
Plasma arginine, µM		
At any time	112	572 (437–754)
Under treatment[b]	33	400 (290–478)
GVA,[c] µmol/L	27	4.7 (3.2–6.9)
ArgA,[c] µmol/L	27	3.1 (2.2–4.0)
ALT, µmol/L	27	71 (43–156)
Hyperammonaemia,[d] n (%)	92	55 (60)

[a]Unless otherwise stated; [b]Treatment consisted of adopting a protein-restricted diet to limit exogenous arginine intake
[c]Normal GVA and ArgA levels are <0.035–0.280 µmol/L and <0.010–0.160 µmol/L, respectively[4]; [d]Ammonia ≥100 µmol/L
ALT = alanine aminotransferase; ArgA = argininic acid; GVA = α-keto-δ-guanidinovaleric acid; Q = quartile.

Disease Manifestations

- The majority of patients presented with lower-limb spasticity and experienced seizures (**Figure 2**)
- All patients with upper-limb spasticity also reported lower-limb spasticity
- Intellectual disability was moderate/severe in 39% of patients

Figure 2. Commonly reported disease manifestations



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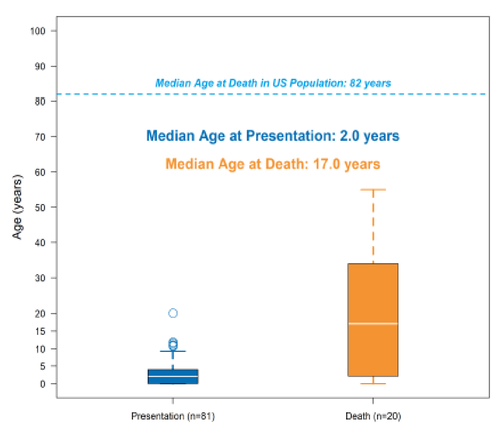
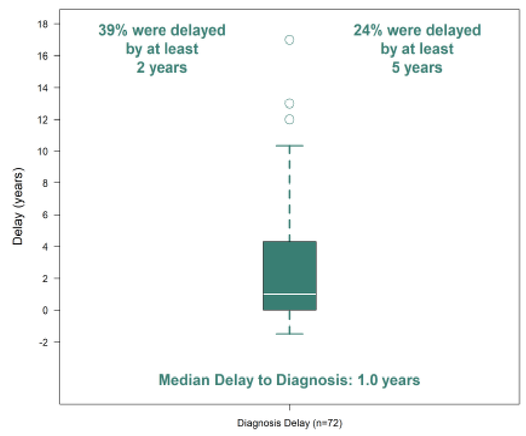
RESULTS (continued)

Diagnosis

- Median age at ARG1-D onset was 2 years and median delay in diagnosis was 1 year (**Figure 3**)
- Twelve patients were identified through newborn screening
- Of the patients not identified using newborn screening, 39% had delays in diagnosis ≥2 years and 24% had delays in diagnosis ≥5 years (**Figure 3)**

Figure 3. Age at disease onset, patients' mortality and median delays in ARG1-D diagnosis





Disease Management

- Management approaches, where cited, included adoption of severe dietary protein restriction (n=97), use of essential amino acid supplements (n=42), and use of ammonia scavengers (n=60)
- Of note, median arginine levels remained above 200 µmol/L, which is the current recommended target treatment guidance level in patients who adopted a protein-restricted diet (**Table 1**)

Mortality

- Of 140 patients included in the analysis, 20 patients had died at the time of the report (median age at time of death was 17.0 years; **Figure 3**)
- Causes of death in this analysis included respiratory complications (n=6), liver complications (n=4), metabolic complications (n=2), hyperammonaemia (n=1), other (n=4). In 3 cases, no information was available

Incorrect Initial Diagnosis

- A number of unique cases with incorrect or incomplete initial diagnosis were identified in literature reports (Table 2)
- In a series of 16 cases from Brazil, some patients were initially diagnosed with cerebral palsy or autosomal recessive hereditary spastic paraplegia[8]

Table 2. Initial diagnoses prior to recognition of ARG1-D

Initial Diagnosis	Age of Initial Diagnosis (yrs)	Age of ARG1-D Diagnosis (yrs)	Reference
Anorexia nervosa and phobic obsessive personality	9	14	Qureshi, 1981
Hypotonic cerebral palsy with mental retardation	2	2	Gambhir, P. 1989
Cerebral palsy	5	9	Scheuerle, A. 1993
Cerebral palsy	5	5.33	Scheuerle, A. 1993*
Generalized epileptic seizures	0.25	9.5	Amayreh, W. 2014
Global developmental delay, failure to thrive	0.83	1.08	Lal, V. 2017
Transverse myelitis	4	5	LeeLavathi, V. 2013
Partial growth hormone deficiency	3.58	10	Cai, X. 2018
Spastic diplegia type of cerebral palsy	3	20	Tsang, J. 2012
Dyslexia (age 5), attention deficit hyperactivity disorder (age 7)	5	14	Bakhiet, M. 2018
Cerebral palsy and seizure disorder	0.67	11	Jichlinski, A 2017

CONCLUSIONS

- ARG1-D is a severe, progressive disease that presents in early childhood with prominent neurological manifestations that significantly impact daily functioning
  - Neurological manifestations include spasticity, cognitive impairment, and/or seizures
- Delays in diagnosis of 5 years or more were common
  - Lack of disease awareness and cases with incorrect diagnosis suggest that the prevalence of ARG1-D is higher than previously estimated
- Increased disease awareness and plasma arginine measurement in patients presenting with spasticity, cognitive impairment, or seizures may lead to earlier diagnosis with better outcomes
- Current disease management fails to substantially impact the marked elevations in plasma arginine levels, leading to continued disease progression, worsening impairment in daily functioning, diminished quality of life, severe disabilities, and early death
- Emerging data from clinical trials demonstrate the potential of a human enzyme-based approach to improve plasma arginine control with accompanying evidence of improvements in important disease related manifestations in patients with ARG1-D

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DATA SOURCES

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* Not included in the initial case report analyses

Disclosures

GAD has received compensation for advisory board activies for Aeglea and has received support for clinical trial sponsored by Aeglea; **NL** is a consultant and receives support for clinical trials from Aeglea; **JLM** has received support for clinical trials from Aeglea; **GB**, **SLP**, **MWB**, and **JEW** are employees and own shares in Aeglea BioTherapeutics, Inc.

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