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Diagnosis and Long-Term Treatment of Arginase 1 Deficiency

Barbara K. Burton, MD

Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

Northwestern Medicine®

Ann & Robert H. Lurie Children's Hospital of Chicago®

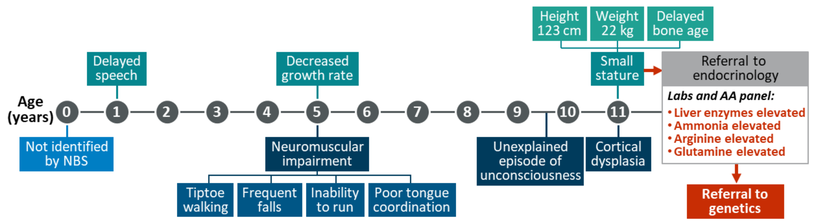
Introduction

- Arginase 1 Deficiency (ARG1-D) is a rare inborn error of metabolism caused by mutations in the *ARG1* gene that compromise arginase enzyme activity, leading to persistent high arginine levels that drive development and progression of neurocognitive and neuromuscular manifestations[1-4]
  - Onset of clinical manifestations typically becomes evident in the first years of life, rather than the first days or weeks as is typical of other urea cycle disorders[2,5]
  - Progressive spasticity, particularly affecting the lower extremities, is a hallmark of ARG1-D. Developmental delay, including missed milestones, as well as short stature, loss of milestone attainment, and intellectual disability are also common[5,6]
- Timely diagnosis and initiation of treatment to reduce arginine is essential to improving patient outcomes
  - The current standard of care for ARG1-D relies on dietary protein restriction with essential amino acid supplementation to minimize arginine intake while maintaining nutritional status. Many patients also receive nitrogen scavengers to reduce risk of hospitalization owing to hyperammonemia[5]
  - Available management strategies for ARG1-D rarely achieve recommended plasma arginine levels, and patients continue to experience significant morbidity. Nonetheless, even when suboptimal, reduction of arginine and cumulative arginine toxicity is important for delaying or diminishing progression of manifestations and may promote clinical stabilization
- This case describes a Hispanic female who was diagnosed with ARG1-D at 11 years of age after referral to genetics and who has since been followed for nearly 15 years

Medical History (Birth to Genetics Referral)

- The patient's medical history and clinical profile upon presentation led to initial suspicion of cerebral palsy. Observation of small stature led to referral to endocrinology, and after comprehensive biochemical testing the patient was referred to genetics **(Figure 1)**
  - The patient was born in Ecuador and not identified by newborn screening, likely because of limited access or program implementation
  - Delayed speech was observed at 12–13 months of age. By age 5 years, decreased growth and multiple indicators of neuromuscular impairment were evident
  - Suspicion of a metabolic disorder and subsequent genetics referral occurred after basic labs and amino acid testing revealed abnormalities consistent with a urea cycle disorder

Figure 1. **Medical History and Observations Leading to Genetics Referral**



ARG1-D Diagnosis and Treatment

- Presence of lower-limb hyperreflexia and tight heel cords, along with other neuromuscular manifestations, cortical dysplasia evident on MRI, intellectual disability, and short stature were felt to be consistent with either cerebral palsy or a metabolic disorder. Biochemical and genetic testing was pursued to reach a definitive diagnosis **(Figure 2)**
  - At the time of presentation to genetics, the patient's plasma arginine was nearly 6-fold the upper limit of normal, indicating a likely diagnosis of ARG1-D. Additional biochemical observations consistent with ARG1-D included slightly elevated glutamine and mild hyperammonemia **(Table 1)**
  - Enzyme assay revealed red blood cell arginase activity of 0.1 µmol/h/mg hemoglobin (normal range, 2–7 µmol/h/mg), further supporting a likely diagnosis of ARG1-D
  - Genetic sequencing revealed a homozygous novel ARG1 variant (c.371-A>G; active site D124G, predicted deleterious), confirming a definitive diagnosis of ARG1-D

Figure 2. **Diagnosis of ARG1-D**

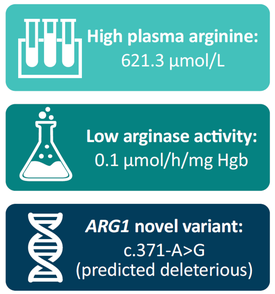


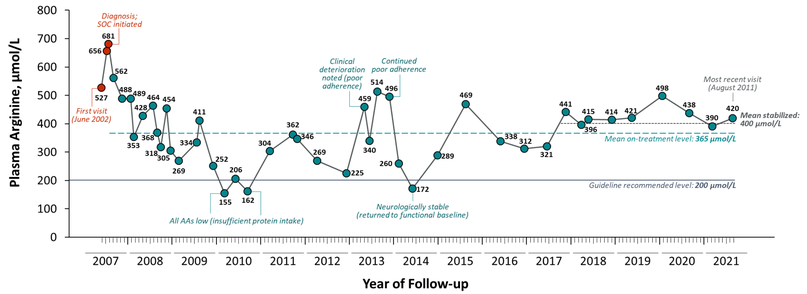
Table 1. **Relevant Biochemistry Before Treatment vs After 14 Years on Treatment**

Analyte (normal range)	Pre-treatment (Jul – Aug 2007)			Last on-treatment follow-up (Aug 2021)
Liver enzymes				
ALT (2–30 µmol/L)	130			Normal
AST (11–35 µmol/L)	67			Normal
ALP (60–320 IU/L)	402			Normal
Key amino acids*				
Arginine (40-115 µmol/L)	527	656	681	420
Glutamine (254–823 µmol/L)	884	999	875	648
Ammonia (11-35 µmol/L)	48			67

*Amino acid panels were run 3 times from July to August 2007.
ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

- Upon diagnosis, dietary protein restriction with essential amino acid supplementation and nitrogen scavenger therapy were initiated
  - Plasma arginine has been lowered from pretreatment levels but remains high and was more than twice the recommended level of ≤200 µmol/L[4] at the most recent visit (420 µmol/L; **Table 1**)
  - Plasma arginine fluctuated considerably, particularly during the first several years of treatment. Levels have been relatively stable over the past 4 years at a mean of 400.3 µmol/L **(Figure 3)**
    - There was a brief period in the patient's early teens in which arginine was <200 µmol/L; however, all amino acids were abnormally low at this time and the patient did not have adequate protein intake
- Notably, the patient has demonstrated acute worsening of neurologic manifestations during episodes of markedly increased plasma arginine **(Figure 3)**. Signs of clinical deterioration include slurred speech, impaired coordination, and worsening of gait abnormalities
  - These episodes generally have been triggered by nonadherence to treatment
  - MRI evaluation showed no changes
  - Reinforcing adherence to treatment resulted in reduction of plasma arginine accompanied by clinical improvement and a return to the patient's functional baseline

Figure 3. **Long-Term Plasma Arginine Time-Course**



Long-Term Outcomes

- At >14 years of follow-up, the patient, now 25 years of age, is generally clinically stable and remains both verbal and ambulatory **(Table 2)**; however:
  - Plasma arginine remains persistently high
  - Cognitive impairment has persisted and progressed, and the patient cannot live independently
  - Neuromuscular involvement in the form of toe walking and spasticity has persisted and varies in severity despite introduction of baclofen and botulinum toxin

Figure 3. **Long-Term Response to Treatment**

Profile	Long-term treatment outcomes
Overall	• Generally stable
Biochemical	• Liver enzymes normalized • **Arginine remains markedly elevated (~400 µmol/L)** • **Ammonia is variable**
Cognitive	• Remains verbal • **Persistent, evolving impairment**
Neuromuscular/mobility	• Remains ambulatory • Persistent gait abnormalities • Persistent spasticity

Summary and Conclusions

- The patient presented with manifestations and medical history consistent with ARG1-D but also common in cerebral palsy, which was initially suspected. Small stature and a complex clinical profile prompted further evaluation, and the patient was quickly and definitively diagnosed with ARG1-D through biochemical and genetic testing
- Chronic high arginine is known to lead to progression of cognitive and neuromuscular manifestations in ARG1-D. Occurrence of acute clinical deterioration associated with transient increases in plasma arginine further demonstrates the role of arginine as the driver of these manifestations
- Early diagnosis and initiation of treatment to lower plasma arginine is critical for decreasing or delaying progressive worsening of manifestations
  - Many of this patient's manifestations were established and had progressed before diagnosis at the age of 11 years
  - The degree of arginine reduction achieved for this patient with available treatment, although far above guideline-recommended levels,[4] is clinically significant, and she remains both verbal and ambulatory at the age of 25 years
- The current standard of care does not adequately lower plasma arginine, as illustrated by persistent high levels and continued progression for this patient, and there is an urgent need for more effective interventions

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