Arginine: The Key Driver of Pathophysiology and Progression in Arginase 1 Deficiency

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Arginase 1 Deficiency: A Distinct Urea Cycle Disorder

- Arginase 1 Deficiency (ARG1-D) is a rare, progressive inborn error of metabolism and distinct urea cycle disorder (UCD) that results in persistent hyperargininemia and debilitating cognitive and mobility impairments.
  - Mutations in ARG1 lead to impaired or absent arginine 1 activity and accumulation of arginine and arginine metabolites (Figure 1).
  - The classic phenotype of ARG1-D involves insidious onset with symptoms becoming evident in the first years of life and progressing over time (Figure 2).
  - Hyperammonemia is a potentially life-threatening complication of most UCDS; however, symptomatic hyperammonemia is relatively uncommon in ARG1-D.
  - The distinct clinical profile of ARG1-D suggests an alternative biochemical driver of disease pathology compared with other UCDS.

Figure 1. Urea Cycle Dysfunction in Arginase 1 Deficiency

Figure 2. Typical ARG1-D Phenotype

Infancy (birth to 1 year)  Toddler age (2–5 years)  Childhood (5–10 years)

- Initial 6–12 months often uneventful.
- May present with:
  - Seizures
  - Episodes of hyperammonemia with irritability, feeding difficulties, poor appetite, nausea/vomiting, decreased alertness
- Spasticity in lower limbs (mainly tiptoe walking)
- Seizures (usually generalized tonic clonic)
- Developmental delay and/or intellectual disability (e.g., delay or interruption of developmental milestones)
- Spontaneous avoidance of high-protein foods (common)
- Progressive spasticity
- Variable decline in growth
- Variable neuromotor decline and worsening of intellectual disability
- Gait abnormalities
- Decrease in vocabulary or loss of spoken language

Management of ARG1-D

- Persistently elevated arginine, >300 μmol/L (normal, <115 μmol/L), is typical in ARG1-D.
- Guideline-recommended plasma arginine (≤200 μmol/L) is rarely achieved with available management strategies.
- Urea Cycle Disorder Consortium (UCDC) data revealed that nearly all on-treatment arginine levels were >115 μmol/L; very few were ≤200 μmol/L.
- Continued progression of ARG1-D is observed despite standard-of-care treatment (e.g., worsening spasticity, gait abnormalities, and ultimately, loss of ambulation).
- Management of other UCDs is focused on reducing risk of hyperammonemia; this is not sufficient to prevent progression and improve long-term outcomes in patients with ARG1-D.