Arginase Deficiency: Natural History, Diagnostic Testing & Treatment

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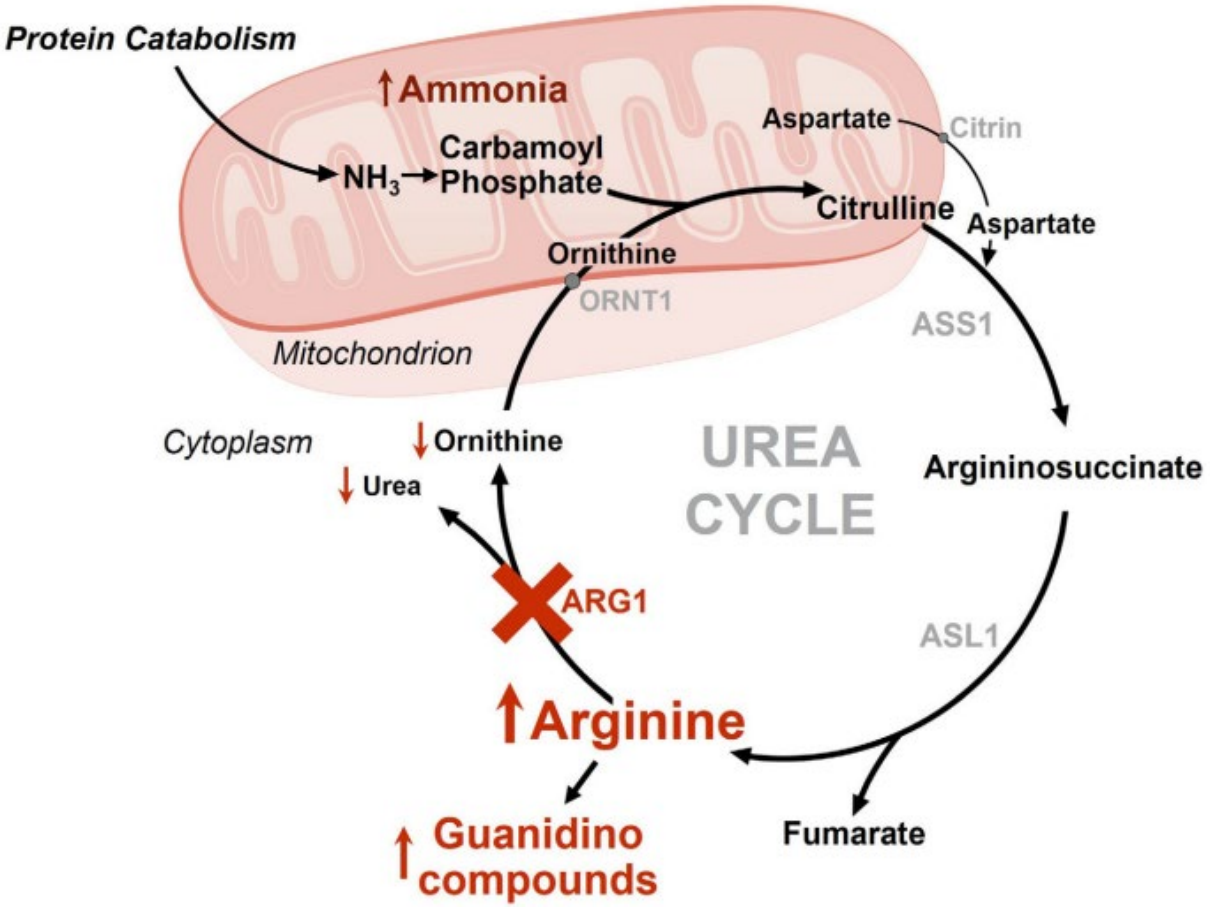
Disclosures

Neither myself nor any member of my immediate family has a financial relationship or interest that related to the content of this discussion.

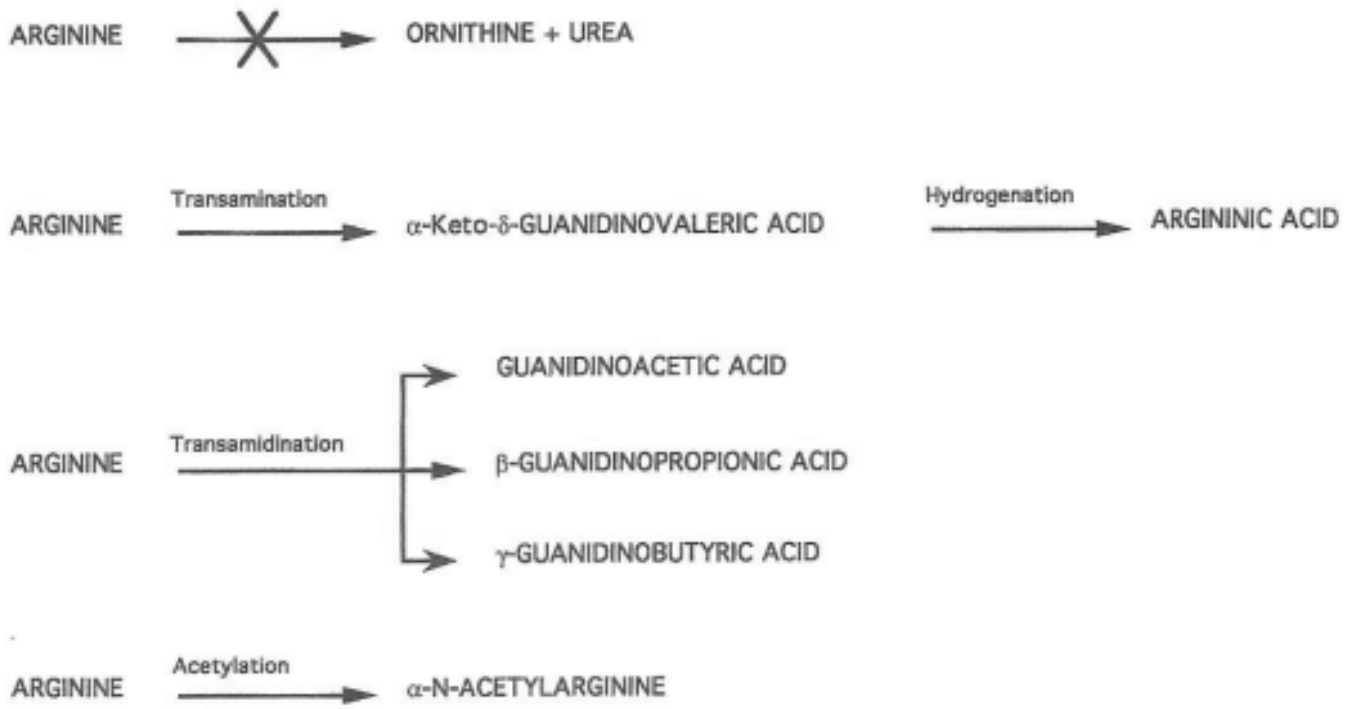
Background on Arginase Deficiency

- *ARG1* encodes for the 6th and final enzyme of the urea cycle
- Autosomal recessive inheritance
- Prevalence
  - To date, > 260 individuals have been identified
  - Estimated global incidence1:726,000 (PMID 35236361)



PMID: 36175366

Pathogenesis **distinct** from other urea cycle disorders (due to elevated arginine rather than hyperammonemia)



By the time a diagnosis has been made based on a symptomatic presentation, irreversible injury to the central nervous system has already ensued.

De Deyn, PP.; Marescau, B.; Qureshi, IA., et al. Hyperargininemia: a treatable inborn error of metabolism?. De Deyn, PP.; Marescau, B.; Qureshi, IA.; Mori, A., editors. John Libbey & Company Ltd.; London, England: 1997. p. 53-69.

Presentation

- Newborns typically asymptomatic

- Symptoms are insidious in onset and become apparent in early childhood (1- 3 years of age) & are progressive without treatment
  - Development of progressive spasticity in lower extremities (80-90%)
    - Often misdiagnosed as cerebral palsy
  - Plateauing of cognitive development (80%) w/ eventual loss of milestones
  - Seizures (60-75%)
  - Growth failure including slowing of linear growth (50-60%) & microcephaly
  - Feeding difficulties (50-60%)
  - Intermittent hyperammonemia (typically with illness)
  - Intermittent liver dysfunction

Diagnosis

- Biochemical Testing:
  - Measurement of plasma arginine level on plasma amino acid analysis
    - Not specific to arginase deficiency

- Genetic Testing: Analysis of *ARG1* gene
  - Single gene, multigene panel, broad genomic sequencing
  - >98% variants identified via sequence analysis, <2% identified via deletion/duplication analysis
  - Known genotype-phenotype correlations:
    - C.466-2A>G, c.77delA, c.263_266delAGAA, c.647_638ins32, p.Ile8Lys, p.Gly106Arg are associated with severe phenotypes

  - Measurement of Arginase Enzyme Activity Level
    - Residual enzyme activity appears to correlate with phenotype

Treatment

a) Reduction of arginine levels (goal < 200 umol/L)

1) Dietary restriction of arginine accomplished via restriction of natural (arginine-containing) dietary protein & supplementation with synthetic arginine free essential amino acid formula
   - Requires close dietary monitoring

2) “Ammonia Diversion Therapy: Use of nitrogen scavenging medications (sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate)

b) Monitoring for/management of acute hyperammonemia

1) Outpatient management – “sick day” formula/feeding plan, supportive care
2) Inpatient management – IV dextrose fluids, IV intralipids, nitrogen scavenging medications

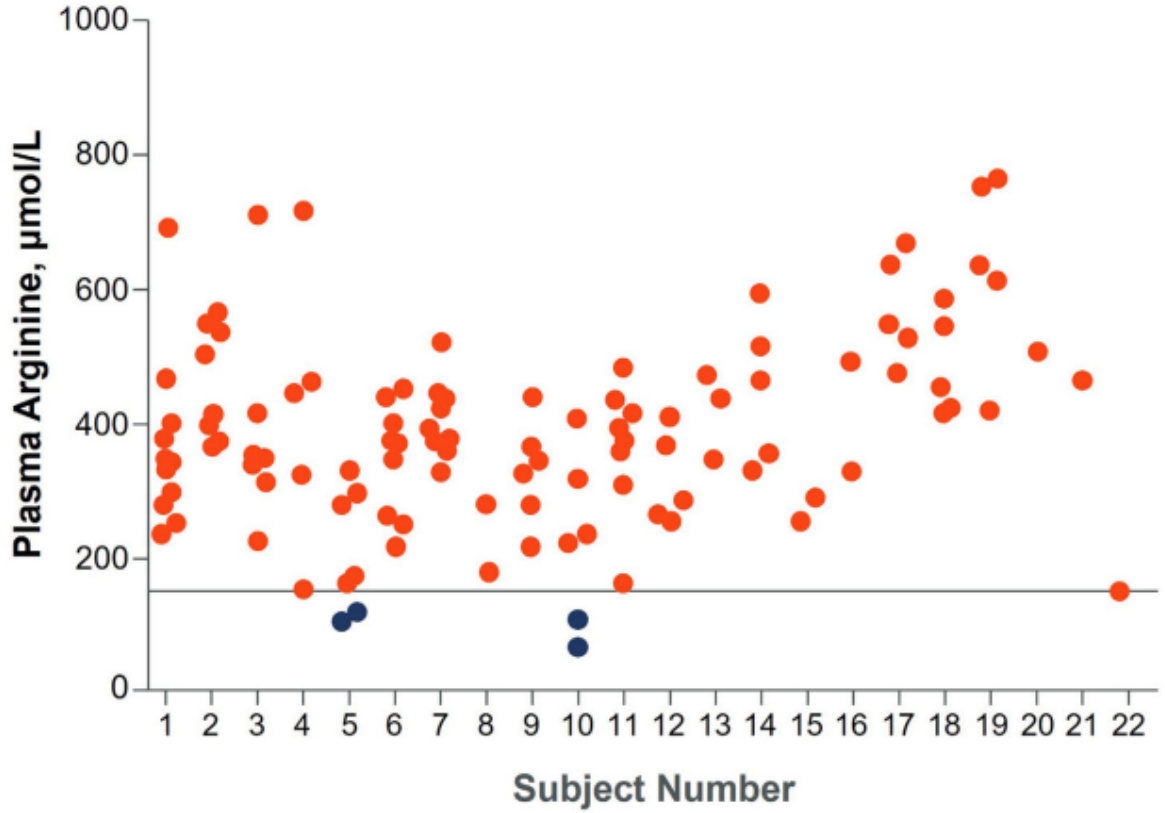
c) Symptom management

1) Referrals to neurology, rehabilitation medicine, physical/occupational/speech therapies as needed

Current therapies available lower but do not normalize arginine levels

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

Figure (PMID 36175366)



Clinical Efficacy – Effects of (just) lowering arginine

(PMID 36175366)

Review article described 6 individuals diagnosed symptomatically (age range: 3 yr 7 mo through 15 years)

- 3 individuals severely affected at the time of diagnosis (ID, minimal to no speech, poor receptive communication skills, non-ambulatory)
  - → demonstrated significant improvement in ADLs (activities of daily living) with treatment
  - →regained self-help skills, improved alertness, improved language, improved spasticity and mobility
- 3 individuals with mild-moderate symptoms (mild delays, hyperactivity, abnormal gaits)
  - →demonstrated improved ataxia, decreased hyperactivity, improved cognitive, 1 patient gained ability to ambulate independently, run, ride a bike and climb stairs

Long-term outcomes: Room for improvement in individuals diagnosed symptomatically

- Review of 22 individuals with arginase deficiency receiving standard of care management (PMID: 26358771)
  - **Median age at diagnosis 3.25 years**
  - Median age at most recent visit 14.74 years
  - 89% of individuals had some degree of developmental delays or intellectual disability
  - 53% had abnormal reflexes
  - 63% had abnormal tone
  - 60% were non-ambulatory

- Review of 19 individuals with arginase deficiency receiving standard of care management (PMID: 27038030)
  - 16 individuals diagnosed symptomatically
  - **Mean age at diagnosis 80 months, median 48 months**
  - 14 individuals reported to have cognitive impairment at most recent follow-up
  - 15 individuals reported to have lower limb spasticity at most recent follow-up

“Long”-Term Outcomes in individuals diagnosed pre-symptomatically

- 38 states screening for Arginase deficiency as of 2017
  - MA earliest in 1999
  - 22 cases identified (out of ~29,000,000 births)
  - Limited publications detailing LT outcomes

- 4 individuals diagnosed pre-symptomatically and started on treatment in the perinatal period. (PMID 36175366)
  - Normal physical, neurological and developmental assessment at 2.5 years
  - 3 individuals all symptom-free at last follow-up (Btwn ages 1 – 3 years)

- Case report of 1 individuals diagnosed on CA NBS who is asymptomatic at 6 years of life (PMID 19562505)

Future Perspectives

- Enzyme replacement therapy PMID: 33325055 & 26358771
  - Phase 2/3 trial completed.
  - Weekly Pegzilarginase (AEB1102) normalized plasma arginine levels in 50% of study participants
  - 79% of participants exhibited clinical improvement on at least one of three assessments of mobility after 20 doses
  - Pending FDA approval.
- mRNA therapy (animal models) PMID: 3150133
- Gene therapy (animal models) PMID: 23388701

Summary of existing literature and limitations

- Arginase deficiency is partially treatable with the clinical tools that are currently available
- Even a partial reduction in arginine has a clear & meaningful impact on the disease course
- Long-term follow-up of individuals diagnosed pre-symptomatically is limited; however, based on the pathogenesis of disease, there is reason to believe that early treatment is superior to delayed initiation of treatment.

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