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The Epidemiology, Methods of Diagnosis, and Clinical Management of Patients With Arginase 1 Deficiency (ARG1-D): A Systematic Review

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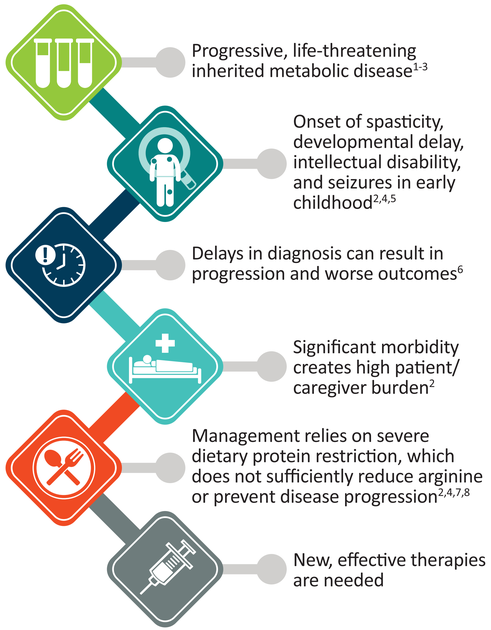
Introduction

- Arginase 1 Deficiency (ARG1-D) is a progressive, debilitating inherited metabolic disease caused by pathogenic mutations in the *ARG1* gene that result in impaired arginase 1 activity and lead to high arginine levels (**Figure 1**)[1-3]
  - ARG1-D is an ultra-rare urea cycle disorder[3]
  - Characteristic manifestations include spasticity, developmental delay, intellectual disability, and seizures[2,4,5]
  - There are currently no approved therapies specifically for ARG1-D
- Limited awareness and recognition of ARG1-D can lead to delays in diagnosis and treatment[6]
- The **objective** of this systematic literature review was to assess published studies describing the epidemiology, diagnosis, and management of patients with ARG1-D

Figure 1. **ARG1-D Overview**



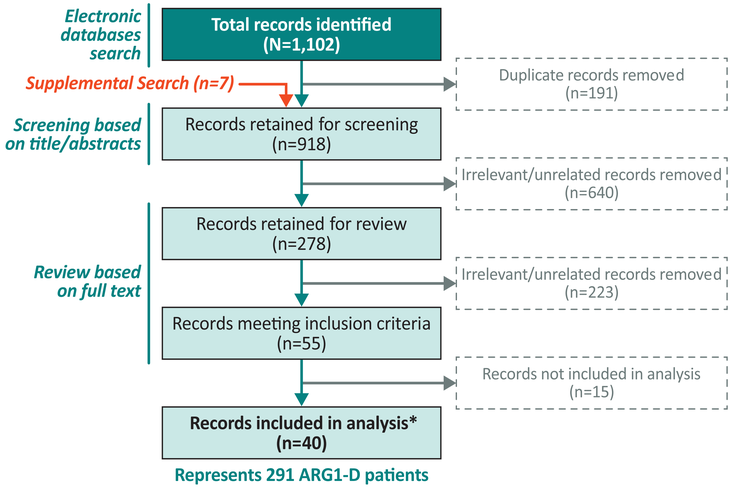
Methods

- Systematic literature review
  - Terms: ARG1-D, argininemia, hyperargininemia, and urea cycle disorders/synonyms
  - Seven databases searched: EMBASE, MEDLINE, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, NHS Economic Evaluation Database, and EconLit
  - Conducted in accordance with Cochrane, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and US Food and Drug Administration (FDA) guidelines
  - Protocol registered in PROSPERO database (ID CRD42020212142)
- Records screened/assessed and data extracted by 2 independent individuals
  - Eligibility and extraction determined by predefined population, intervention, comparison, outcome, timing, and study design (PICOTS) criteria
  - Study quality assessed using Newcastle-Ottawa Scale

Results

- A total of 40 studies describing 291 ARG1-D patients were included in the analysis (**Figure 2**)
  - Cohort studies, n=21
  - Cross-sectional studies, n=19

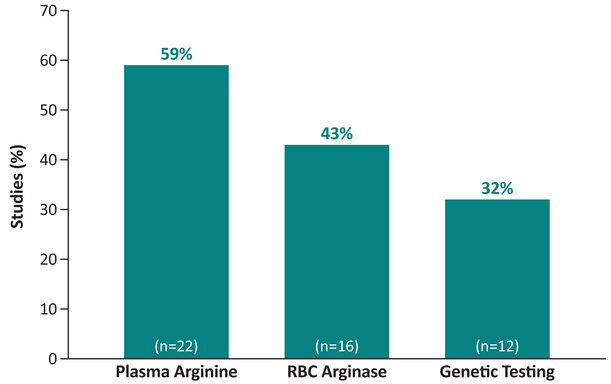
Figure 2. **PRISMA Flow Diagram**



*Rated as good quality per Newcastle-Ottawa scale.

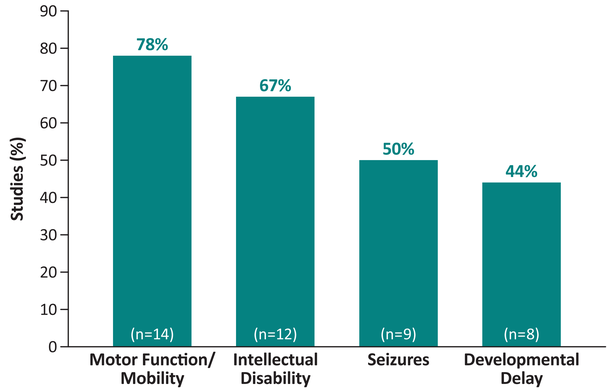
- Median ARG1-D prevalence was 1 per 1,000,000 births
  - Epidemiology was reported in 9 studies
- Plasma amino acid analysis (ie, elevated plasma arginine) was the most commonly reported method of diagnosis (**Figure 3**)
  - Diagnostic approaches were described in 37 studies
  - Twelve studies (32%) included newborn screening

Figure 3. **Diagnostic Methods**



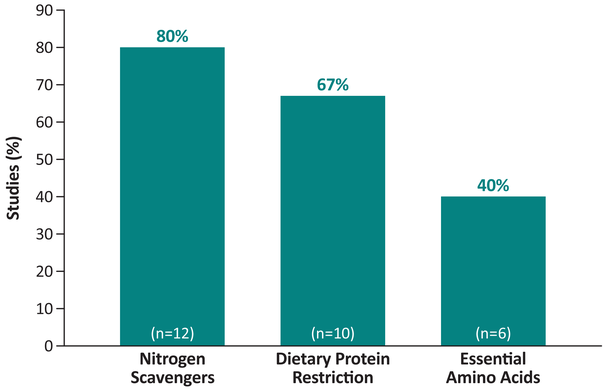
- Motor function/mobility (including the hallmark feature of spasticity) was the most commonly reported manifestation (**Figure 4**)
  - Clinical manifestations were reported in 18 studies
  - Reporting of measures of disease progression was variable across studies
  - The most frequently assessed outcomes were motor function, intellectual disability, and mortality (data not shown)

Figure 4. **Manifestations**



- Nitrogen scavengers and dietary protein restriction were the most commonly reported treatment approaches (**Figure 5**)
  - Treatment approaches were reported in 15 studies
  - Although no clinical practice guidelines specific to ARG1-D were identified, protein intake is addressed in the most commonly cited treatment recommendations relevant to ARG1-D[7,9,10]

Figure 5. **Treatment Approaches**



Conclusions

- The findings of this systematic review support previous publications and observations and illustrate the large unmet need in ARG1-D
- Despite standard-of-care approaches (dietary protein restriction, nitrogen scavengers, and essential amino acid supplementation), the majority of patients experience debilitating manifestations such as spasticity, loss of mobility, intellectual disability, and seizures
- There is limited published literature describing treatment, outcomes, and practice guidelines for this ultra-rare disorder

References **1.** Carvalho DR, et al. *Gene*. 2012;509(1):124-130. **2.** Carvalho DR, et al. *Pediatr Neurol*. 2012;46(6):369-374. **3.** Sun A, et al. 2020; https://www.ncbi.nlm.nih.gov/books/NBK1159/. **4.** Amayreh W, et al. *Dev Med Child Neurol*. 2014;56(10):1021-1024. **5.** Bakhiet M, et al. *Medicine (Baltimore)*. 2018;97(20):e10780. **6.** Huemer M, et al. *J Inherit Metab Dis*. 2016;39(3):331-340. **7.** Haberle J, et al. *J Inherit Metab Dis*. 2019;42(6):1192-1230. **8.** Burrage LC, et al. *Hum Mol Genet*. 2015;24(22):6417-6427. **9.** World Health Organization. 2007; https://apps.who.int/iris/handle/10665/43411. **10.** Summar M and Tuchman M. *J Pediatr*. 2001;138(1 suppl):S6-10.