Presented at the 14th International Congress of Inborn Errors of Metabolism • November 21 – 23, 2021 • Sydney, Australia

Arginase 1 Deficiency (ARG1-D) Presenting With Clotting Abnormalities

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Introduction and Objective

- Arginase 1 Deficiency (ARG1-D) is a rare, debilitating inherited metabolic disease with significant morbidity driven by persistent high arginine levels[1-4]
- Disease manifestations typically begin to develop in early childhood and progress over time[1,2]
  - Progressive spasticity, most commonly affecting the lower limbs, is a hallmark of ARG1-D[1]
  - Other common manifestations include seizures, intellectual disability, developmental delay, and failure to thrive[5]
  - Patients may also exhibit food avoidance and/or vomiting[6]
- Early detection and treatment of ARG1-D is essential for delaying or decreasing progression and has been shown to have a positive impact on patient outcomes later in life[2,3]
- The aim of this presentation is to describe a patient with ARG1-D who presented with an atypical profile and was definitively diagnosed through whole-exome sequencing 2 years after initial presentation

Presentation and Initial Assessments

- The patient is a female of Hispanic descent who presented to acute care at 9 years of age because of new-onset seizures
  - Upon admission, global developmental delay, intellectual disability, failure to thrive, and short stature were evident
  - Nosebleeds and prolonged prothrombin time prompted referral to hematology for further evaluation
- Several abnormalities were detected during workup **(Table 1)**. Vitamin K deficiency was considered but the patient's prolonged prothrombin time did not decrease upon oral or subcutaneous vitamin K administration
  - Suspicion of a vitamin K receptor disorder prompted referral to genetics

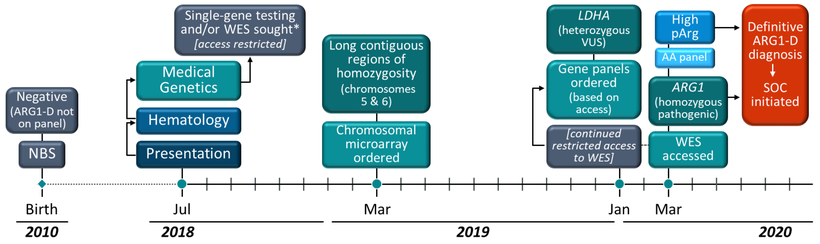
Table 1. **Key Labs at Presentation**

Analyte	Result	Value (Reference Range)
Complete blood count	Normal	Not applicable
Hepatic enzymes		
Alanine transaminase	High	138 U/L (0–37 U/L)
Aspartate aminotransferase	High	182 U/L (0–65 U/L)
Clotting tests		
Prothrombin time	High	21.5 s (12.0–14.7 s)
International normalized ratio	High	2.25 (0.85–1.17)
Partial thromboplastin time	High	37.6 s (22.9–35.8 s)
Coagulation proteins		
Factor V	Normal	60% (67–150%)
Factor VII	Low	12% (72–205%)
Factor VIII	High	284% (50–242%)
Factor IX	Low	20% (73–184%)
Factor X	Low	30% (58–135%)
Fibrinogen	Normal	330 mg/dL (230–510 mg/dL)
Thrombin	Normal	16.2 s (15.0–21.2 s)
Fat-soluble vitamins		
Vitamin A	Normal	8.3 mg/L (5.5–13.6 mg/L)
Vitamin E	Normal	1.3 mg/L (0.7–3.9 mg/L)
Vitamin K1	High	4.42 ng/mL (0.13-1.39 ng/mL)

Diagnosis

- Time from presentation to diagnosis was nearly 2 years owing to a combination of the patient's presentation and access to testing **(Figure 1)**
  - An inborn error of metabolism (IEM) was not high on the differential at this time due to the patient's biochemistry and history of normal newborn screens
  - Based on access, chromosomal microarray and gene panels for congenital disorders of glycosylation and comprehensive glycogen storage disease panels were ordered; results did not suggest a diagnosis
  - Whole-exome sequencing ultimately revealed a homozygous pathogenic variant in ARG1 (c.466-G>C), indicating a diagnosis of ARG1-D. Amino acid testing confirmed the ARG1-D phenotype (plasma arginine, 607 µmol/L; reference range, 18–127 µmol/L)

Figure 1. **Diagnostic Journey**

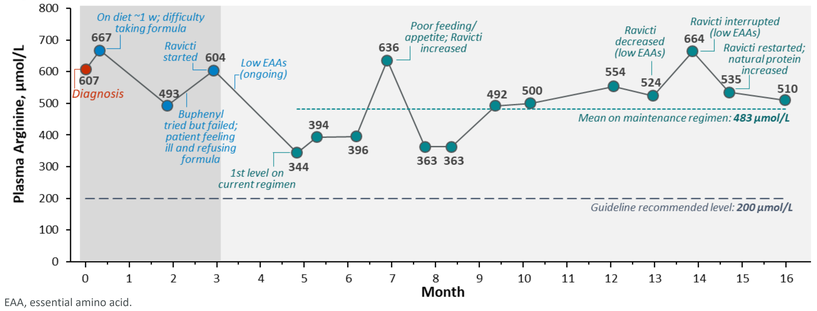


*Genetic testing sought for suspected vitamin K receptor disorder and other phenotypic features.
NBS, newborn screening; pArg, plasma arginine, SOC, standard of care; VUS, variant of unknown significance; WES, whole-exome sequencing.

Treatment and Clinical Outcomes

- At diagnosis, the patient's plasma arginine was more than 5 times the upper limit of normal
- Standard-of-care treatment was started, including dietary protein restriction and metabolic formula **(Figure 2)**
  - The patient receives ~50% daily protein from natural foods/supplementation and ~50% from arginine-deficient amino acid formula
  - An ammonia scavenger (Buphenyl) was started but was poorly tolerated and the patient was subsequently switched to Ravicti
  - During the first several months on the current treatment regimen, plasma arginine was reduced to the mid to high 300s, but essential amino acids (EAAs) were also reduced and remain low despite treatment adjustments

Figure 2. Plasma Arginine Time Course



EAA, essential amino acid.

- Despite the best available treatment, the patient's plasma arginine has not approached guideline-recommended levels
  - Mean plasma arginine on the current treatment regimen is 483 µmol/L
  - Recent plasma arginine levels have been in the low to mid 500s
- Although plasma arginine remains high, implementation of standard-of-care management has improved the patient's clinical profile through nearly 1.5 years of follow-up
  - Food avoidance and vomiting have diminished
  - Eating and growth have increased
  - There have been no further hospitalizations or seizures
  - Cognitive impairment remains evident but has not worsened over time

Typical and Atypical Features of Clinical Phenotype

- This patient presented with both common and uncommon manifestations of ARG1-D; her clinical profile at presentation did not raise suspicion of an IEM but, combined with her medical history, was consistent with ARG1-D in retrospect **(Figure 3)**
  - Lower limb spasticity is a hallmark manifestation of ARG1-D but remains absent in this patient
  - Clotting abnormalities such as those observed in this patient are rare in ARG1-D but have been reported in some patients

Figure 3. **Comparison of ARG1-D Profile With Present Case**

Medical History and Clinical Profile	ARG1-D	Present Case
Healthy at birth	✓	✓
Spasticity	✓	⊘
Gait abnormalities and/or neuromotor decline	✓	⊘
Seizures	✓	✓*
Developmental delay	✓	✓
Cognitive impairment and/or intellectual disability	✓	✓
Food refusal and/or protein avoidance	✓	✓
Periodic vomiting	✓	✓†
Failure to thrive	✓	✓
Short stature	✓	✓
Global developmental delay	✓	✓
Symptomatic hyperammonemia	⊘	⊘
Abnormal clotting	⊘	✓
Genetic and Biochemical Profile	**ARG1-D**	**Present Case**
Suspected consanguinity	✓	✓
Homozygous *ARG1* mutation	✓	✓
High plasma arginine	✓	✓
Elevated transaminases	✓	✓
Dysregulated clotting factors	⊘	✓

*Prompted presentation to acute care; no seizure recurrence.
†Reported by caregiver after ARG1-D diagnosis.

Summary and Conclusions

- Although this patient lacked some characteristic manifestations of ARG1-D and exhibited nonspecific manifestations and clinical signs considered rare in ARG1-D, her overall medical history and clinical profile are consistent with her ARG1-D diagnosis[5,7,8]
- Clotting abnormalities are rare in ARG1-D; however, consideration of ARG1-D (or another IEM) when patients present with unexplained hematologic abnormalities may improve accurate diagnosis
- Diagnosis could have been made readily and earlier though newborn screening if ARG1-D had been included on the panel or through amino acid testing had ARG1-D been suspected at presentation
- This case emphasizes several key areas of need in ARG1-D awareness and management
  - Clinical improvement and subsequent stabilization reinforce the need for early diagnosis and treatment, including better access to diagnostic testing
  - Lack of spasticity should not rule out the possibility of ARG1-D
  - The persistent elevation of plasma arginine despite standard-of-care treatment reinforces the need for new therapies

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Disclosures **Dr Farach** has served as a consultant for Aeglea. **Dr Brown** has no relationships to disclose.

Acknowledgments Medical writing support was provided by Heather Starkey, PhD, from The Curry Rockefeller Group, LLC (Tarrytown, NY), and was funded by Aeglea.