ICIEM 2021

14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM

21–23 NOVEMBER 2021, SYDNEY, AUSTRALIA

Diagnosis of Arginase 1 Deficiency in a Patient With Cerebral Palsy

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Introduction

- Arginase 1 Deficiency (ARG1-D) is a rare, inherited urea cycle disorder (UCD) with progressive, debilitating manifestations driven by persistent high arginine levels[1-4]
  - Some inborn errors of metabolism, including ARG1-D and other UCDs, present with neurologic/neuromotor disorders and may be treatable[5]
- Manifestations of ARG1-D typically become evident early in childhood and progress over time[2,6]
  - Spasticity, particularly affecting the lower limbs, is a distinguishing feature of ARG1-D compared with other UCDs; additional common clinical manifestations include developmental delay, intellectual disability, seizures, and short stature[6,7]
  - Episodes of hyperammonemia are common in most UCDs but are comparatively less frequent and less severe in ARG1-D; however, hyperammonemia does occur in ARG1-D and can be triggered by stressors such as infections[4,8]
- Clinical manifestations common to ARG1-D and cerebral palsy (CP) include, but are not limited to, failure to thrive, delayed/missed milestones, seizures, and spasticity, which can complicate diagnosis[9]
- There are no therapies approved specifically for ARG1-D. The current standard of care (SOC) relies on dietary protein restriction with essential amino acid supplementation and use of nitrogen scavengers[6]
  - The normal plasma arginine range, based on analysis of the large Framingham Cohort, is 40–115 µmol/L[10]; the guideline-recommended level for patients with ARG1-D is ≤200 µmol/L[4]
  - Current SOC does not adequately reduce plasma arginine levels, and long-term outcomes are poor.[6] Nonetheless, timely implementation of SOC is important to reduce arginine toxicity and risk of hyperammonemia

Objective

- To describe the medical history, presentation, diagnosis, and management of a patient with CP and subsequently diagnosed with concurrent ARG1-D

Case Study

Medical History

- The patient is a 5-year-old female born in Honduras and living in Texas with a history of meningitis that led to numerous debilitating symptoms and a subsequent diagnosis of CP
  - Generalized stiffness and posturing were evident from the time of the meningitis insult
  - Seizures typically last 3–5 minutes and involve stiffening of upper and lower extremities with a postictal phase lasting 5–6 minutes
- At 4 years of age, the patient's antiepileptic medication was changed from phenobarbital to levetiracetam. Levetiracetam was poorly tolerated, and the dose was subsequently reduced

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Case Study, cont'd

Presentation and Workup

- Approximately 6 weeks after the first acute care visit, the patient presented with a 2-week history of increased seizures, vomiting, and food avoidance as well as increased fussiness and decreased wet diapers and was hospitalized (**Figure 1**)
- Initial workup identified several physical and biochemical abnormalities (**Table 1**) that prompted a series of specialty consults

Figure 1. **Case Summary: Presentation, Inpatient Course, and Diagnosis**

Patient History

Prior history included:
- Acute care presentation (4 y of age, May 2020) with cough and nasal congestion
  - **Seizure medication changed** from phenobarbital to levetiracetam
- **Meningitis (2 mo of age)** and subsequent:
  - Spastic quadriplegia
  - Seizures
  - Failure to thrive
  - Global developmental delay
  - Cognitive impairment (nonverbal)
  - Scoliosis
  - **Diagnosis of cerebral palsy**

June 14, 2020

Acute Care Admission

Presented with 2-w history of:
- Increased seizure frequency
- Vomiting TID
- Decreased oral intake and bottle refusal

Treatment and supportive measures at admission:
- Levetiracetam for seizures
- Fed with soft foods/formula
  - Upon admission, mother reported long-time history of choking while feeding
- Wheelchair dependent
  - Mobility milestones not attained

June 14–23, 2020

Inpatient Course and Diagnosis

Initial Workup
- UTI (Klebsiella)
- Elevated liver enzymes
- Hyperammonemia

Specialty consults

Orthopedics
- Severe broad-based scoliosis (45°)
- Lumbar lordosis
- Bilateral coxa valga and hip dysplasia
- Chronic right hip dislocation (reduced)

Neurology
- Posturing considered consistent with opisthotonos (levetiracetam increased)
- EEG: primary generalized epilepsy
- MRI: extensive encephalomalacia attributed to prior bilateral MCA infarcts

Pediatric Surgery
- Nasogastric feeding tube placed

Genetics
(due to hyperammonemia and transaminitis)
- Spasticity, failure to thrive, vomiting, hyperammonemia, and seizures considered consistent with a UCD
  - **Spasticity** suggested ARG1-D
- Amino acid panel: pArg=670 µmol/L
  - **Elevated pArg (~6× upper limit of normal range)** indicated ARG1-D
- Genetic testing: ARG1 c.466-1G>C
  - Homozygous **pathogenic *ARG1* variant** confirmed ARG1-D

ARG1-D SOC initiated

ALT, alanine transaminase; AST, aspartate aminotransferase; EEG, electroencephalography; MCA, middle cerebral artery; MRI, magnetic resonance imaging; pArg, plasma arginine; SOC, standard of care; TID, three times daily; UCD, urea cycle disorder; UTI, urinary tract infection.

Table 2. **Initial Laboratory Evaluation**

Workup	Result	Workup	Result*
Complete blood count	Normal	Urinalysis	Positive
Glucose	Normal	**Aspartate aminotransferase**	**High**
Calcium	Normal	**Alanine transaminase**	**High**
Sodium	Normal	Alkaline phosphatase	High
Bicarbonate	Normal	Thyroid-stimulating hormone	High
Chloride	Normal	Free thyroxine	High
Blood urea nitrogen	Normal	**Glutamine**	**High**
Creatinine	Normal	**Blood ammonia**	**High†**

*Unless otherwise indicated, abnormal findings during initial workup subsequently normalized. †Potentially triggered by *K. pneumoniae* urinary tract infection.

Diagnosis

- Genetics was consulted and a UCD was suspected (**Figure 1**)
  - Amino acid testing revealed significantly elevated plasma arginine, suggesting a diagnosis of ARG1-D
  - Genetic testing revealed a known pathogenic variant in the *ARG1* gene, confirming the ARG1-D diagnosis

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Case Study, cont'd

Treatment and Follow-Up

- SOC was implemented and the patient has been followed through 8 months. Plasma arginine is decreased but remains high; her manifestations are not improved but she is clinically stable

June 2020–February 2021

Follow-Up

At 8 mo on treatment:

- Patient generally clinically stable
  - No functional improvement evident (likely due to existing brain insult)
- pArg improved but remains elevated
- Ammonia levels decreased across repeat assessments
- Liver enzymes generally normalized
  - 1 occurrence of uptrending AST and ALT
- 2 occurrences of hospitalization associated with:
  - 1 occurrence of UTI
  - 1 occurrence of hyperammonemia

ALT, alanine transaminase; AST, aspartate aminotransferase; pArg, plasma arginine; UTI, urinary tract infection.

Summary and Conclusions

- This patient's neurologic manifestations, which resulted at least in part from perinatal insult and subsequent CP, may have masked development or worsening of manifestations of her ARG1-D
- This case demonstrates the importance of additional biochemical workup in patients with a clinical diagnosis of CP, particularly when presentation suggests a more complex condition
  - Vomiting, food avoidance, and hyperammonemia suggested a UCD; spasticity narrowed the suspected diagnosis to ARG1-D
  - Amino acid testing offers a simple, fast, and cost-effective method of screening for ARG1-D and other UCDs that can be confirmed through genetic testing
- In summary, this patient's diagnosis of CP was upheld and a coinciding diagnosis of ARG1-D was established, indicating both environmental and genetic causes for her debilitating manifestations and providing an opportunity to enhance her care

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