Movement Disorders
CLINICAL PRACTICE

CASE SERIES WITH LITERATURE REVIEW

Arginase 1 Deficiency in Patients Initially Diagnosed with Hereditary Spastic Paraplegia

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Abstract: Background: Arginase 1 Deficiency (ARG1-D) is a rare autosomal recessive urea cycle disorder (UCD) characterized by pathologic elevation of plasma arginine and debilitating manifestations. Based on clinical commonalities and low disease awareness, ARG1-D can be diagnosed as hereditary spastic paraplegia (HSP), leading to treatment delays.

Cases: A Hispanic woman with unremarkable medical history experienced progressive lower-limb spasticity in her 20s and received a diagnosis of HSP. She developed significant gait abnormalities and is unable to walk without assistance. More recently, two Hispanic brothers with childhood-onset manifestations including lower-limb spasticity, developmental delays, and seizures presented with suspected HSP. All three patients were ultimately diagnosed with ARG1-D based on plasma arginine several-fold above normal levels and loss-of-function *ARG1* variants. Disease progression occurred before ARG1-D was correctly diagnosed.

Literature Review: Retrospective analyses demonstrate that diagnostic delays in ARG1-D are common and can be lengthy. Because of clinical similarities between ARG1-D and HSP, such as insidious onset and progressive spasticity, accurate diagnosis of ARG1-D is challenging. Timely ARG1-D diagnosis is critical because this UCD is a treatable genetic cause of progressive lower-limb spasticity.

Conclusions: Arginase 1 Deficiency should be considered in HSP differential diagnosis until biochemically/genetically excluded, and should be routinely included in HSP gene panels.

Arginase 1, the final enzyme in the urea cycle, catalyzes arginine conversion into ornithine and urea. The urea cycle disorder (UCD) Arginase 1 Deficiency (ARG1-D) is a rare autosomal recessive inborn error of metabolism (IEM) caused by mutations in the *ARG1* gene, on chromosome 6q23, that result in impaired or absent enzymatic activity and subsequently, pathologic elevation of arginine.[1] Symptomatic hyperammonemia is less common/severe in ARG1-D than other UCDs,[2,3] and persistently high levels of arginine and guanidino compounds (potentially toxic arginine metabolites) and oxidative stress are proposed to play a role in ARG1-D pathophysiology.[4–8]

Arginase 1 Deficiency is progressive and debilitating, with a variety of neurologic manifestations that typically develop in late infancy or early childhood and worsen over time.[3,9] The most common clinical presentation includes spasticity, global developmental delay, intellectual disability, and seizures.[10] Progressive lower-limb spasticity is the hallmark feature of ARG1-D.[1,8] This often manifests between 1 to 5 years of age and may present as hyperreflexia, clonus, and toe walking or other gait abnormalities. Over time, worsening lower-limb spasticity can lead to inability to walk independently or loss of functional mobility.[11] Cognitive impairment and adaptive behavior deficits are also common. Patients may miss key developmental milestones or experience gradual regression/loss of milestones after normal early neurodevelopment. Approximately 60% to 75% of patients experience seizures,[12,13] which have a wide range of onset (4 months–30 years)[14] and have been shown to correlate with elevated arginine and arginine metabolites.[7,8]

Owing to the typical presence of lower-limb spasticity and the insidious onset, nonspecific nature, and slow progression of other manifestations, ARG1-D can be initially diagnosed as

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neurologic disorders such as cerebral palsy (CP) or hereditary spastic paraplegia (HSP), delaying diagnosis of the UCD.[14–18] HSP comprises a group of rare monogenic disorders; to date, >80 distinct forms and >60 implicated genes have been identified.[19] Like ARG1-D, HSP results in slowly progressing lower-limb spasticity and weakness. Hyperreflexia and extensor plantar response (Babinski reflex) are often present in both disorders. Whereas uncomplicated/pure HSP is characterized by lower-limb spasticity and weakness, complex forms involve a range of additional neurologic manifestations (eg, developmental delay, cognitive impairment). Several childhood-onset complex forms of HSP, such as the four adaptor protein complex 4 (AP-4)–associated HSPs (SPG47, SPG50, SPG51, and SPG52), also present with seizures.[20]

Importantly, ARG1-D is one of the few treatable causes of progressive lower-limb spasticity. In a review of 27 cases of confirmed ARG1-D, spasticity was reported in 23, with most presenting with late-onset spasticity of the lower limbs.[21] Of the 11 patients with treatment outcome reported, spasticity was improved in 7.[21] ARG1-D is not typically considered in the HSP differential diagnosis, and clinical presentation consistent with HSP can delay ARG1-D diagnosis and treatment. Here, we describe three patients with ARG1-D but initially diagnosed with HSP and discuss the scientific literature.

Case Series

Case 1

The proband is a 30-year-old Hispanic woman (El Salvador) with a history of normal growth and development through adolescence, with no significant medical history, vomiting/protein aversion, or hospitalizations. She graduated high school with educational assistance and is fluent in Spanish and English. Interestingly, the patient's family history was notable for an older sister with ARG1-D. The sister had normal birth and development until 10 years of age when she was hospitalized for metabolic decompensation. Seizures and increasing lower-limb spasticity at this time prompted biochemical testing that led to diagnosis of ARG1-D. The proband had later onset of manifestations and a prolonged diagnostic odyssey. She developed mild leg weakness and occasional unprovoked falls at age 20, followed by progressive lower-limb weakness and gait deterioration over the next 4 years. At 24 years, she was referred by her primary care physician to neurology for further work-up. Mild elevation of ammonia was observed at this time (54 μmol/L; reference range, 13–40 μmol/L). Magnetic resonance imaging (MRI) of the spine was normal; however, MRI of the brain showed mild cortical atrophy (Fig. 1A) and nonspecific fluid-attenuated inversion recovery hyperintensities in the bilateral frontal periventricular white matter (Fig. 1B). Based on her family history, ARG1-D was highest on the diagnostic differential and nitrogen scavengers (sodium phenylbutyrate and lactulose) were initiated, but dietary protein restriction, the mainstay of ARG1-D management,[3,22] was not discussed. One year later (age 25 years), continued decline and increased lower-limb spasticity prompted additional evaluation. Excretion of uracil and orotic acid was increased, and plasma amino acid testing revealed markedly elevated plasma arginine (404 nmol/mL; reference range, 32–120 nmol/mL) and low levels

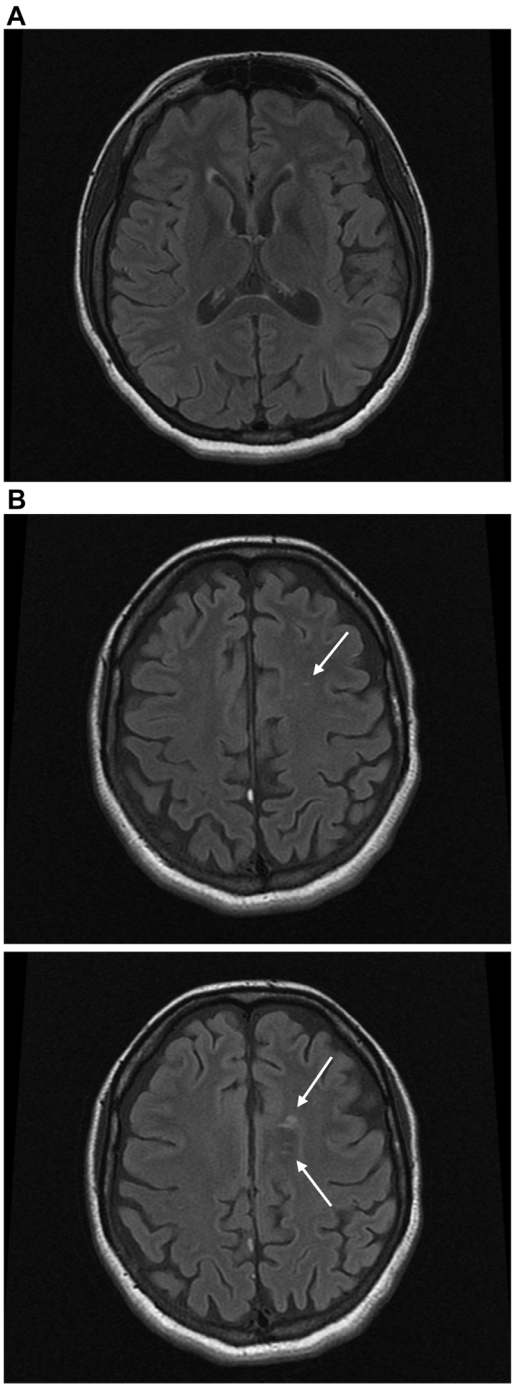

FIG. 1. MRI of the brain (case 1; age 24 years) showing (A) mild cortical atrophy and (B) nonspecific T2 FLAIR hyperintensities (arrows). MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery.

of nearly all other amino acids. The nitrogen scavengers were discontinued at this time because of lack of clinical benefit, and alternative genetic diagnoses, including spinocerebellar ataxia, mitochondrial disorders, and HSP, were proposed. HSP was the default diagnosis over the next 2 years with no mention of an arginine metabolism disorder in her medical record.

The proband was definitively diagnosed with ARG1-D at age 27 years when she accompanied her sister to a metabolic genetics clinical visit. The sister's diagnosis and the patient's historical plasma arginine level (documented in her chart) suggested ARG1-D. Genetic testing confirmed a homozygous loss-of-function *ARG1* variant [NM_000045.4(ARG1):c.466-1G>C]. A low-protein diet with essential amino acid supplementation was prescribed, but marked lower-limb spasticity and gait abnormalities persisted (Video 1). She subsequently enrolled in a clinical trial evaluating an investigational human enzyme therapy.

Case 2

The second case comprises two recently diagnosed brothers of Hispanic origin (El Salvador) with a history of neurologic manifestations. At presentation, the older patient was 11 years of age. Neurocognitive/intellectual manifestations included delayed development at 6 months; specifically, he did not track or interact with toys. Language attainment was achieved by 2 years but he regressed, losing nearly all speech by 6 to 7 years. Neuromuscular/mobility manifestations included hypotonia and inability to sit unassisted until 18 months of age, and push-crawling until 4 years. This patient never attained walking ability. Seizures developed at 4 years, but he has not experienced a seizure in >4 years and is not treated with an anti-epileptic. The younger brother was 8 years of age at presentation, with a similar range of manifestations albeit with different age of onset and degree of severity. Delayed development was evident at 3 months and he has no significant language attainment beyond saying "mama." He did not walk until 2 years and toe walking was evident at this time. He has experienced seizures since age 4 to 5 years, and received treatment with sodium valproate.

These patients presented to neurology in March 2021, at which time significant lower-limb spasticity was noted. MRI revealed thinning of the corpus callosum in both brothers, with moderate diffuse infratentorial and supratentorial volume loss in the older brother and prominent cerebellar atrophy and supratentorial

Video 1. Gait abnormalities in an adult patient with ARG1-D (case 1). The impact of marked lower-limb spasticity in this patient is clearly reflected in gait abnormalities, dependence on assistive devices, and difficulty climbing stairs. She self-selects a gait speed that minimizes the speed-dependent effect of spasticity, which primarily affects her quadriceps and plantarflexor muscle groups. To combat limited knee flexion and dorsiflexion, she utilizes slight hip circumduction to facilitate limb advancement. She also extends her trunk to assist in gaining step length; this is more pronounced without her 4-wheeled walker and shoes.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13612

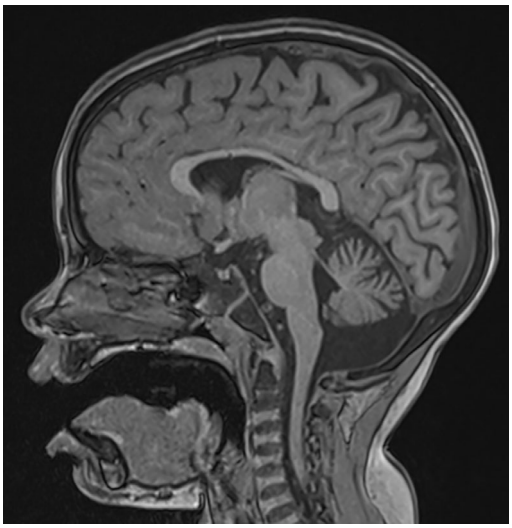

FIG. 2. MRI of the brain (case 2, younger brother; age 8 years) showing thinning of the corpus callosum and decreased cerebellar volume. MRI, magnetic resonance imaging.

parenchymal atrophy in the younger (Fig. 2). Electroencephalography in the younger brother showed abnormal activity in the centroparietal, left temporal, and bioccipital regions. Based on the brothers' prominent spasticity and family history (two paternal aunts with suspected HSP), they were referred to genetics for further evaluation.

Upon presentation to genetics, worsening spasticity, intellectual disability, and growth delay were noted. Plasma arginine was strikingly elevated, at nearly 7-fold of the upper reference limit (older, 848 nmol/mL; younger, 813 nmol/mL), indicating a likely diagnosis of ARG1-D. Targeted *ARG1* analysis identified compound heterozygous pathogenic *ARG1* variants in both patients [NM_000045.4(ARG1):c.466-1G>C and NM_000045.4(ARG1): c.314_345delins(20) p.I105_H115NASIRMT], confirming the ARG1-D diagnosis. Glutamine was elevated for the older brother and normal for the younger, at 969 and 548 μmol/L, respectively (no ammonia levels were available). Dietary protein restriction and nitrogen scavenger treatment were initiated for both patients. At diagnosis, daily protein intake was twice the prescribed goal level in the older brother and >5-fold the prescribed goal in the younger; this high protein diet suggests a lack of protein aversion. The younger brother was switched from sodium valproate (a known mitochondrial inhibitor) to levetiracetam for his seizures.

Literature Review and Discussion

Arginase 1 Deficiency is one of the rarest UCDs, accounting for an estimated 3.5% of these disorders and with a global prevalence of only 1:726,000.[23,24] Delays in diagnosis are well-documented and can result from lack of recognition of ARG1-D due to its rarity or initial suspicion of other neurologic disorders because of similarities in clinical features.[11] For example, in a multinational retrospective study of 19 patients, ~80% of whom had established lower-limb spasticity, there was a mean delay of >4 years from onset of manifestations to ARG1-D diagnosis.[12] Similarly, among 16 Brazilian patients with ARG1-D, the first manifestation was lower-limb spasticity for 75% of the cohort.[25] Several patients were initially diagnosed with CP or HSP, and the mean delay to diagnosis of ARG1-D ~10 years.[25] In a more recent analysis of 140 published cases of ARG1-D, 84% of patients had lower-limb spasticity and 42% had gait abnormalities.[11] Initial diagnoses reported were wide-ranging and included CP and spastic diplegia, and one quarter of patients had a diagnostic delay ≥5 years.[11]

Arginase 1 Deficiency and HSP have been described as genetic disorders with characteristic spasticity that can mimic CP.[8,14,15,17,21] ARG1-D is also a recognized genetic mimic of HSP (particularly complex HSP), and, importantly, is treatable.[18,21,26,27] ARG1-D is not the only treatable IEM that can present clinically as HSP. Adrenoleukodystrophy, biotinidase deficiency, cerebrotendinous xanthomatosis, and the UCD hyperornithinemia-hyperammonemia-homocitrullinuria syndrome also present with spasticity (often progressive), developmental delay, intellectual disability, and/or cognitive impairment, and seizures/epilepsy.[3,15,18,21,26,27] Structural abnormalities of the central nervous system are reported in ARG1-D and other IEMs with pyramidal signs as well as in childhood-onset complex HSP. Neurologically, HSP is characterized by retrograde degeneration of the long axons of the corticospinal tracts and posterior columns of the spinal cord, and corticospinal tract degeneration has been reported in ARG1-D.[28] Cortical and cerebellar atrophy and a thin corpus callosum have also been reported in these disorders and may contribute to neurologic manifestations.[15,20,29–32] Thinning of the corpus callosum, as was observed in the two brothers (case 2), has been reported in numerous forms of complex HSP, including SPG11, SPG15, SPG18, SPG21, SPG35, SPG46, SPG48, SPG54, SPG56, and the AP-4–associated forms.[15] In one study of 156 patients with AP-4–associated HSP, a thin corpus callosum was evident in 90%.[20]

Variability in severity of manifestations and rate of progression and lack of clear genotype/phenotype association in ARG1-D contribute to the challenges in recognition and diagnosis, as seen in the three patients described here despite sharing a known pathogenic *ARG1* variant. At diagnosis, the female patient (case 1) had plasma arginine in the low 400 nmol/mL range; the two brothers (case 2) were more than twice that, in the low to mid 800s. She did not develop overt manifestations until adulthood, whereas the two brothers showed obvious signs as early as 3 to 6 months. In all three patients, the presence of lower-limb spasticity led to suspicion of HSP and delayed diagnosis of ARG-D, and mobility impairments were established by the time of accurate diagnosis. There is growing awareness in the literature surrounding the risk of missed or delayed diagnosis of ARG1-D, and several

reports include recommendations that IEMs, and ARG1-D in particular, be considered in the differential diagnosis for patients with slowly progressing neurologic manifestations or neurologic regression, especially when progressive spasticity is present.[15,27,33–35] Specifically, the challenge of identifying ARG1-D in patients with manifestations characteristic of HSP has been addressed.[25] Features suggesting ARG1-D include pronounced worsening of spasticity and avoidance of high-protein foods, but interestingly, the latter was not apparent in the patients described here.[25] Biochemical and genetic testing in addition to clinical evaluation and consideration of patient/family history is necessary to correctly diagnose these disorders.

Arginase 1 Deficiency can be readily diagnosed through quantitative plasma amino acid analysis and confirmed via erythrocyte arginase 1 enzymatic activity assays or genetic testing for *ARG1* variants. Accurate molecular diagnosis is essential to ensure timely treatment initiation and access to emerging therapeutics, such as a human enzyme therapy for ARG1-D currently in ongoing clinical trials.[36,37] Awareness of potential alternate diagnoses and the need for confirmatory biochemical/genetic testing is particularly important because HSP is not included in newborn screening recommendations and ARG1-D is included only as a secondary condition,[38] with inconsistent criteria and implementation.[39] Although the availability of and access to whole genome or exome sequencing has led to a shift toward increasing adoption of these technologies as the diagnostic method of choice for HSP in some institutions, particularly for childhood-onset complex HSP, gene panels continue to be the mainstay of HSP diagnosis in other centers or healthcare systems. Among seven large commercial genetic testing laboratories in the United States, only five include *ARG1* on HSP panels, limiting the likelihood of identifying possible ARG1-D when HSP is suspected. Including *ARG1* on all HSP gene panels could reduce risk of delays in ARG1-D diagnosis and treatment initiation.

Conclusions

The prominence of lower-limb spasticity and similarity of manifestations between ARG1-D and complex HSP can lead to delayed diagnosis of ARG1-D owing to lack of disease awareness and variability of presentation. As demonstrated by these patients and the broader scientific literature, this leads to disease progression and worse clinical outcomes because of delayed treatment. Negative consequences of delayed treatment initiation because of delayed or incorrect diagnosis are widely recognized; however, failure to correctly diagnose ARG1-D can also lead to inappropriate treatment. In the case of the brothers described here, the younger patient received sodium valproate to manage seizures for years, which can worsen mitochondrial function–dependent disorders such as ARG1-D. ARG1-D should be considered as a differential diagnosis until biochemically/genetically excluded when HSP is suspected, and also included on standard HSP gene panels.

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Author Roles

(1) Patients: A. Clinical Workup and Diagnosis, B. Mobility Assessment. (2) Manuscript Preparation: A. Conceptualization of the Work, B. Writing of the First Draft, C. Review and Critique, D. Approval to Submit.

M.C.M.: 1A, 2A, 2B, 2C, 2D.

N.F.: 1B, 2C, 2D.

G.G.: 1A, 2C, 2D.

Disclosures

Ethical Compliance Statement: Patient evaluation, diagnosis, and treatment were conducted in compliance with the ethical standards and practices of UT Southwestern Medical Center. Patient consent was not required for this work, with the exception of one patient who was video recorded to allow qualitative assessment of her gait abnormalities; this patient provided written informed consent for video recording and inclusion of a de-identified video clip within this manuscript. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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