Infancy (2–5 years)1-5

consistent with the literature, the patient described in this case

Childhood (5–10 years)1-5

• Urinary urgency

Table 1. Differential Characteristics of ARG1-D vs HSP

Avoidance of high-protein food  ✔ ✘
Seizures  ✔

We report a patient who was undiagnosed or misdiagnosed as having HSP for

in the last step of the urea cycle (Figure 1)

ARG1-D causes progressive spastic diplegia, which typically manifests in early childhood. Other manifestations include developmental delay, intellectual disability, and seizures.✔ (Figure 2)

Based on the paper, the patient was 24 years old at diagnosis. She presented with leg weakness and recurrent falls, and had very long-chain fatty acids (VLCFAs) within normal limits. She also had moderately elevated ammonia (54 µmol/L) but only mildly elevated urea (2.4 mmol/L) and mild hyperammonemia (107 µmol/L).

The patient was treated with sodium phenylbutyrate and lactulose, which helped reduce ammonia levels. However, the patient continued to have symptoms, and treatment with the nitrogen scavenger sodium phenylbutyrate and lactulose was initiated. Despite treatment, the patient was still experiencing some symptoms at the time of the paper's publication.

The patient is currently enrolled in a clinical trial of an investigative therapy, pegylated human arginase, a human enzyme-based approach to lower plasma arginine levels.

Conclusions

Previous reports have described misdiagnosis of ARG1-D with spastic diplegia as HSP, largely owing to similarities in neurological presentation.]

• Consistent with the literature, the patient described in this case report was misdiagnosed for multiple years despite her family history of ARG1-D, allowing establishment and progression of typical manifestations of the disorder

Because ARG1-D (unlike HSP) is a treatable cause of spastic paraplegia, there is a continued need for increased awareness of the disease among healthcare providers and improved recognition of when both biochemical and genetic testing should be performed.

Informal Consent: The patient provided informal consent and data were collected under an investigational protocol approved by the institutional review board of UT Southwestern Medical Center.

Acknowledgments: The authors thank MW Bechter for his contributions to this work. Editorial support was provided by Catherine Diddle, PhD, of Carle Rockwood Group, LLC (Tarrytown, NY), and was funded by Angiogenesis Biologics, Inc. (Austin, TX).

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Table 1. Differential Characteristics of ARG1-D vs HSP

<table>
<thead>
<tr>
<th>ARG1-D</th>
<th>HSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal arginine, ammonia, and urea</td>
<td>✔</td>
</tr>
<tr>
<td>Analysis of high protein food</td>
<td>✔</td>
</tr>
<tr>
<td>Seizures</td>
<td>✔</td>
</tr>
<tr>
<td>Urinary arginine</td>
<td>✔</td>
</tr>
</tbody>
</table>

We report a patient who was undiagnosed or misdiagnosed as having HSP for >3 years before being diagnosed with ARG1-D.

Clinical Presentation

A 24-year-old woman presented with a 4-year history of slowly progressive leg weakness and recurrent falls (Figure 3). Testing revealed elevated plasma arginine (404 nmol/mL; Table 2).

In biochemical evaluations

• Very long-chain fatty acids were normal

• Urine organic acids identified increased uracil and orotic acid excretion

Because of her family history (an older sister with a diagnosis of ARG1-D based on biochemical testing), ARG1-D was considered high on the diagnostic differential and treatment with the nitrogen scavenger sodium phenylbutyrate and lactulose was initiated.

At a neurological follow-up, it was noted that the patient should be evaluated for biotinidase deficiency, vitamin E deficiency, or arginase deficiency. The default diagnosis was HSP.

Testing revealed elevated plasma arginine (404 nmol/mL; Table 2).

At a subsequent neurological follow-up, the patient had continued to decline with progression of lower-extremity spasticity, and underwent additional evaluation for potential causes of these symptoms. At this time, treatment with the nitrogen scavenger and lactulose was stopped owing to lack of clinical benefit.

Despite the patient’s family history, HSP was the suspected diagnosis for >2 years, with no discussion of a disorder of arginine metabolism as the primary diagnosis in the patient’s medical record.

In conclusion, we report a patient who was undiagnosed or misdiagnosed as having HSP for >3 years before being diagnosed with ARG1-D.

Diagnosis of ARG1-D

• At age 27, the patient accompanied her sister to a visit with a geneticist provider and was subsequently diagnosed with ARG1-D during a metabolic genetics clinical visit based on biochemical data, family history, and homocysteine loss-of-function mutations (rs1064794165) in the ARG1 gene.

• Following diagnosis of ARG1-D, the patient was placed on a regimen of severe protein restriction and treated with an esmolol acid supplementation and a nitrogen scavenger (sodium phenylbutyrate). Attempts to lower plasma arginine levels were not sufficiently effective (Table 3).

Table 3: Serum Arginine Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Arginine, nmol/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-Jun-2015</td>
<td>145 (200–570)</td>
</tr>
<tr>
<td>06-Jan-2016</td>
<td>139 (150–560)</td>
</tr>
<tr>
<td>01-Jun-2017</td>
<td>139 (150–560)</td>
</tr>
<tr>
<td>21-Jun-2018</td>
<td>139 (150–560)</td>
</tr>
</tbody>
</table>

The patient was referred to neurology, where magnetic resonance imaging (MRI) of the spine was normal, but MRI of the brain revealed nonspecific, fluid-attenuated inversion recovery hyperintensities in the bilateral frontal periventricular white matter and mild cortical atrophy.

Figure 4: MRI of the Brain Showing (A) Mild Cortical Atrophy and (B) Nonspecific T2-FLAIR Hypointensities

Figure 4. MRI of the Brain Showing (A) Mild Cortical Atrophy and (B) Nonspecific T2-FLAIR Hypointensities

• Variable decline in growth

• Feeding difficulties, poor appetite, nausea/vomiting, decreased drankness

• Increased plasma arginine is the hallmark of ARG1-D, arginine levels may be 3.5- to 10-fold higher than those in unaffected individuals. If ARG1-D is suspected, diagnosis can be confirmed via plasma arginine levels, through genetic testing, or through enzymatic assays for red blood cell arginase activity.

• Delays in diagnosis or misdiagnosis often occur because of lack of disease awareness and differences in patient presentation.

• Although hyperammonemia occurs in many urea cycle disorders, severe hyperammonemia is less frequently seen in ARG1-D, and manifestations of the disorder are driven by persistently elevated arginine.

• ARG1-D may be misdiagnosed as hereditary spastic paraplegia (HSP) because both disorders are characterized by progressive lower-extremity spastic paraparesis.

• In biochemistry evaluations

• Only mild elevation of ammonia (54 µmol/L) was observed

• Both B12, copper, and vitamin E levels were normal

• Very long-chain fatty acids were normal

• Urine organic acids identified increased uracil and orotic acid excretion

• Because of her family history (an older sister with a diagnosis of ARG1-D based on biochemical testing), ARG1-D was considered high on the diagnostic differential and treatment with the nitrogen scavenger sodium phenylbutyrate and lactulose was initiated.

• At a neurological follow-up, it was noted that the patient should be evaluated for biotinidase deficiency, vitamin E deficiency, or arginase deficiency. The default diagnosis was HSP.

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