Clinical Case Report

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Argininemia as a cause of severe chronic stunting and partial growth hormone deficiency (PGHD)

A case report

Xiaotang Cai, MD[a,b], Dan Yu, PHD[a,b], Yongmei Xie, MD[a,b], Hui Zhou, MD[a,b,*]

Abstract

Rationale: Argininemia is an autosomal recessive inherited disorder of the urea cycle. Because of its atypical symptoms in early age, diagnosis can be delayed until the typical chronic manifestations – including spastic diplegia, deterioration in cognitive function, and epilepsy – appear in later childhood.

Patient concerns: A Chinese boy initially presented with severe stunting and partial growth hormone deficiency (PGHD) at 3 years old and was initially treated with growth hormone replacement therapy. Seven years later (at 10 years old), he presented with spastic diplegia, cognitive function lesions, epilepsy, and peripheral neuropathy.

Diagnoses: Ultimately, the patient was diagnosed with argininemia with homozygous mutation (c.32T>C) of the ARG1 gene at 10 years old. Blood tests showed mildly elevated blood ammonia and creatine kinase, and persistently elevated bilirubin.

Interventions: Protein intake was limited to 0.8 g/kg/day, citrulline (150–200 mg [kg d]) was prescribed.

Outcomes: The patient's mental state and vomiting had improved after 3 months treatment. At 10 years and 9 month old, his height and weight had reached 121cm and 22kg, respectively, but his spastic diplegia symptoms had not improved.

Lessons: This case demonstrates that stunting and PGHD that does not respond to growth hormone replacement therapy might hint at inborn errors of metabolism (IEM). IEM should also be considered in patients with persistently elevated bilirubin with or without abnormal liver transaminase, as well as elevated blood ammonia and creatine kinase, in the absence of hepatic disease.

Abbreviation: PGHD = partial growth hormone deficiency.

Keywords: argininemia, PGHD, stunting

1. Introduction

Argininemia is a rare autosomal recessive inherited disorder of the urea cycle, caused by homozygous or compound heterozygous mutation of the arginase-1 gene (*ARG1*) on chromosome 6q23, which encodes an enzyme called arginase that catalyzes the hydrolysis of arginine to ornithine and urea. ARG1 deficient disorder can affect the liver-based urea cycle; patients exhibit hyperargininemia with spastic paraparesis, progressive neurological and intellectual impairment, persistent growth retardation, and infrequent episodes of hyperammonemia. The estimated prevalence of argininemia is 1 in 1,100,000.[1,2] Unlike patients with other urea cycle defects, patients with argininemia rarely exhibit hyperammonemic encephalopathy. The onset of argininemia is typically insidious, with the symptoms – including spastic paraplegia, mental retardation, failure to thrive, and seizures – arising during childhood.[2–4]

We describe the case of a Chinese patient with argininemia, who initially presented with severe stunting and partial growth hormone deficiency (PGHD) at 3 years old, but was ultimately diagnosed with argininemia with a homozygous mutation (c.32T>C) in the *ARG1* gene at 10 years old. At 10 years old, the patient presented with seizure, dyskinesia, and peripheral neuropathy. Blood tests revealed elevated creatine kinase and blood ammonia, and slightly elevated bilirubin.

2. Case report

The patient was born at 36^{+4} weeks' gestation with a birth weight of 2500 g. Three days after birth, he was hospitalized for several days due to transient hypoglycemia. His developmental milestones were unremarkable before 1 year of age. Following this, his developmental milestones became delayed, for example, the boy began to walk at 1 year and 6 months and his walk was

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[a] Department of Pediatrics, West China Second University Hospital, [b] Key Laboratory of Obstetric and Gynaecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Sichuan University, Chengdu, Sichuan, China.

[*] Correspondence: Hui Zhou, Department of Pediatrics, West China Second University Hospital, Sichuan University, No.20, Section 3, Renmin South Road, Chengdu 610041, Sichuan, China (e-mail: z_hui0832@126.com).

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slower than normal and clumsy. There was no family history of severe childhood illness, death, or stunting. The boy showed a preference for carbohydrate intake from infancy, with a clear aversion to animal proteins and was prone to vomiting. The boy has a sister showing normal development.

The boy presented to our child health clinic at age 3 years and 7 months because of his short stature and excessive thinness. At this time, his height and weight were 86 cm and 12.5 kg, respectively (both were below the 3rd percentile, according to China's 1995 urban 0–18 year-old male height percentiles scale). A neurologic examination focusing on the motor and sensory nervous system and cerebellar function produced unremarkable findings. Laboratory tests revealed retardation of bone age (equivalent to a 1 year old) and mildly elevated total bilirubin (29.4 μmol/L, normal range: 2–24 μmol/L), direct bilirubin (10.4 μmol/L, normal range: 0–7 μmol/L), and indirect bilirubin levels (18.6 μmol/L, normal range: 1.7–17 μmol/L) but normal hepatic enzyme levels. Blood glucose was slightly lower than normal (3.52 mmol/L, normal range: 3.9–6), whereas his electrolytes were normal. Screening tests for hepatitis B and A were negative. A growth hormone excitement test revealed low levels of growth hormone (0 minute: 0.76 ng/mL; 30 minutes: 4.5 ng/mL; 60 minutes: 6.3 ng/mL; 90 minutes: 4.1 ng/mL; and 120 minutes: 1.5 ng/mL). An MRI revealed a normal pituitary gland, and thyroid function was normal. The boy was diagnosed with PGHD and managed accordingly, being treated with growth hormone for about 1 month. No treatment effect was evident. However, he received no follow-up until 10 years of age.

At 10 years old, the boy presented to our pediatric neurological clinic because of a single episode of generalized tonic seizure. The boy had previously had a seizure at 8 years old when receiving tetanus antitoxin treatment after head trauma. During clinic counseling, one of his parents noted that the patient had gait disturbance for almost 1 year, attributed to a persistent tightening of both knee joints. The boy could not jump and easily fell when he ran and walked. The boy, who was in primary school, also showed poor academic performance. At this time, his height and weight were still below the 3rd percentile, at 116 cm and 20.1 kg, respectively. He exhibited no organomegaly. His muscle strength of the low extremities was grade 4 (Oxford Scale), and he showed increased distal muscle tone than normal, hyperreflexia, and a negative Babinski sign. Laboratory tests revealed mildly elevated hepatic enzyme levels, including aspartate transaminase (50.9 IU/L, normal range: 0–50 IU/L) and alanine transaminase (52 IU/L, normal range: 0–45 IU/L), as well as mildly elevated total bilirubin (47.7 μmol/L, normal range: 0–25 μmol/L), direct bilirubin (16.4 μmol/L, normal range: 0–6.8 μmol/L), and indirect bilirubin levels (31.3 μmol/L, normal range: 0–25 μmol/L). His creatine kinase (564.4 IU/L, normal range: 55–190 IU/L) and blood ammonia levels (62.3 mmol/L, normal range: 9–30 mmol/L) were slightly elevated. A urine occult blood test was positive (++). Red blood cells (3–4/HP, normal range: 0–3/HP) were evident in a urine sediment microscopy. Both renal ultrasound and renal function were normal, as were the results of cranial MRI and electroencephalography. A peripheral nerve examination revealed reduced compound muscle action potential (CMAP) of the right peroneal nerve and bilateral tibial nerve, while the right peroneal nerve distal latency was suspected to be prolonged. A muscle biopsy revealed neurogenic lesion (Fig. 1). A gene test was performed and the results demonstrated that he carried compound homozygote mutations of ARG1 (c.32T > C) (Fig. 2). Lee et al[5] and Wu et al[6] reported the mutation, which can lead to argininemia, in South Korea and Chinese populations in 2011 and 2015. Subsequently, his blood and urine amino acid levels were analyzed, revealing a blood arginine concentration of 108.42 μM (normal range: 10–50 μM) as well as elevated urinary excretion of orotic acid; however, his blood citrulline, glutamine, glutamate, and alanine concentrations were normal. His intelligence quotient was lower than normal, at 80. The boy subsequently diagnosed with argininemia.

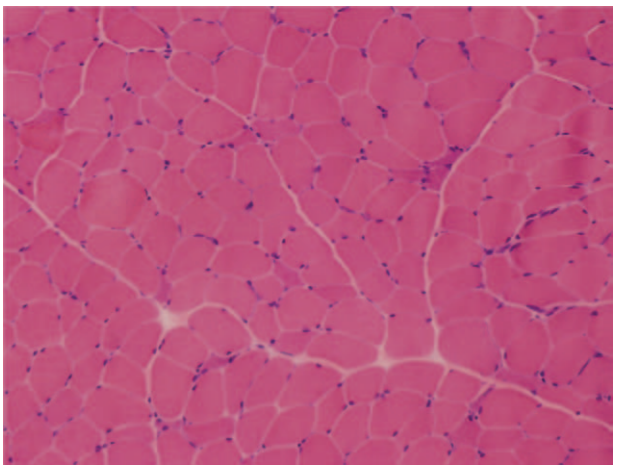

Figure 1. Muscle biopsy results: mild degeneration of muscle fibers, focal muscle fiber regeneration, no lymphocyte infiltration, and no evidence of hyperplasia in fibrous tissues in the muscle (hematoxylin and eosin [HE] staining ×20).

Following the diagnosis, we recommended that the patient begins a low-protein diet (0.8 g/kg/day) to decrease his blood arginine levels, as well as start taking citrulline (150–200 mg/kg/day). His mental state and vomiting had clearly improved after 3 months of this treatment. Laboratory tests conducted again at a local hospital which the following values were obtained (note that the normal ranges used at this hospital slightly differ from those used at our hospital): aspartate transaminase (45 IU/L, normal range: 0–37 IU/L), alanine transaminase (46.1 IU/L, normal range: 0–40 IU/L), total bilirubin (31.9 μmol/L, normal range: 3.4–20.5 μmol/L), direct bilirubin (14.3 μmol/L, normal range: 0–6.8 μmol/L), and indirect bilirubin levels (17.6 μmol/L, normal range: 0–18 μmol/L). His urine occult blood test was positive (+). No red blood cells were evident in his urine sediment microscopy. After 9 months treatment, his height and weight reached 121 cm and 22 kg, but his spastic diplegia symptoms had not improved.

3. Discussion

ARG1 deficiency, or argininemia, is a rare autosomal recessive disorder of ureagenesis with clearly different clinical manifestations from other urea cycle disorders.[2,4,5] Children with argininemia are normal at birth and early childhood, showing chronic manifestations in later childhood along with delayed developmental milestones, including scissoring gait, spastic quadriplegia, deterioration in cognitive function, and epilepsy.[5,7] Among all its manifestations, progressive spastic paraplegia is the most obvious sign. In our case, the final diagnosis was made only after the patient began to exhibit abnormal gait and positive pyramidal signs at the age of 10 years. Early symptoms of the disease are nonspecific, and include developmental retarda-

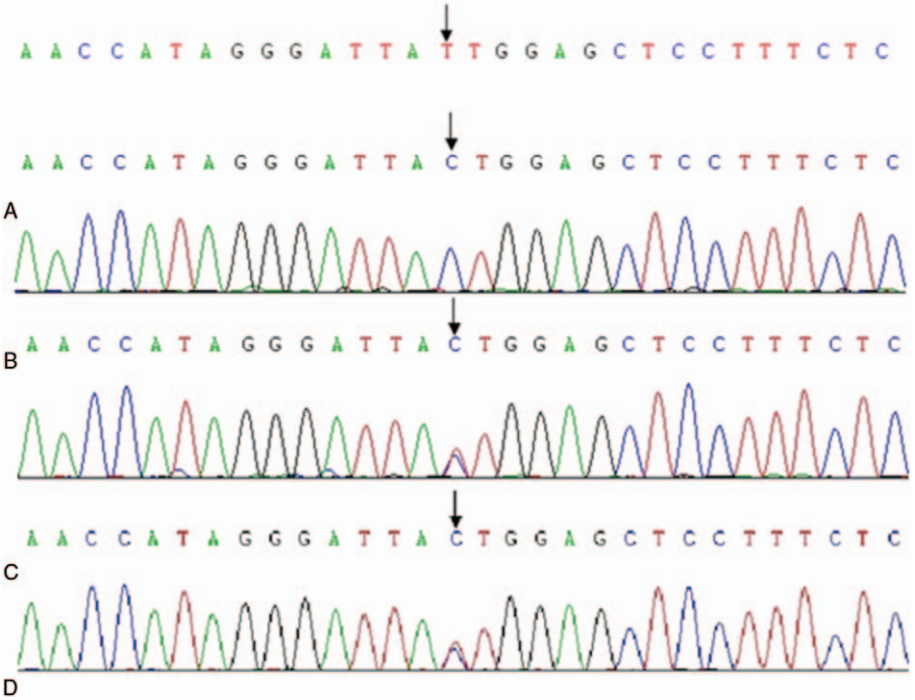

Figure 2. *ARG1* gene test results: A is NCBI reference sequence; B is gene sequence of patient (homozygous, c.32T > C); C is the patient's father's gene sequence (heterozygous, c.32T > C); and D is patient's mother's gene sequence (heterozygous, c.32T > C).

tion, retarded growth, recurrent vomiting, and protein aversion.[8,9] However, the rarity and nonspecific nature of early manifestations of argininemia make it difficult to diagnose without careful clinical examination and long-term follow-up. The patient in this study was taken to our child health clinic at 3 years and 7 months old because of his short stature. Given the child's history of transient hypoglycemia in the neonatal period, abnormal bone age and growth hormone excitement test results, and normal pituitary MRI, thyroid function test, and neurological examination, it was not unreasonable to treat the child for PGHD. In our clinic, stunted children always present with delays in motor and cognitive function. Although our patient exhibited a delayed motor development milestone and mildly elevated bilirubin during a liver function test, all the nonspecific manifestations of argininemia were overlooked because of his neonatal history and lost to follow-up status.

Patients with argininemia almost show a failure to thrive and a persistent low growth rate that leads to a short stature. Both Carvalho et al[8] and Prasad et al[10] reported that around 81% of patients with argininemia showed growth restriction. The growth restriction might relate to the spontaneously self-selected low protein diet during the growth period or by the underlying primary disease.[4] We speculate that the reason for the patient's PGHD was neurological damage during the process of disease development. The pathogenesis of neurological damage in argininemia is currently unclear. Terheggen et al[11] and Cederbaum et al[12] suggested that the chronic accumulation of arginine and its metabolites might play a direct role in the neurological dysfunction observed in argininemia, as they are known to be neurotoxic and epileptogenic.[13,14] Furthermore, patients who control their ammonia levels to normal through protein restriction but still show persistently elevated arginine levels do not typically experience relief. L-Arginine has been shown to induce oxidative stress, which inhibits Na^+–K^+ adenosine triphosphatase activity[15,16] and decreases brain energy metabolism.[17] Guanidino compounds can also lead to demyelination and upper motor neuron signs, as well as inhibit GABAergic neurotransmission.[14] Moreover, arginine and guanidino compounds can influence neuronal survival by inducing free radical defenses and decreasing antioxidant defenses.[3–5] In summary, the pathogenesis of the neurological dysfunction in argininemia may be the result of all its neurological presentations, including PGHD.

Argininemia is characterized by progressive neurologic impairment in the late stage of the disease.[3] In our case, a peripheral nerve examination revealed demyelination and elevated creatine kinase levels, while a muscle biopsy showed neurogenic lesions. All these tests indicated that peripheral nerve damage is part of the neurologic impairment of argininemia. Although peripheral neuropathy has seldom been reported as a clinical feature of argininemia, Tsang et al[18] reported a case of ARG1 deficiency with mixed axonal and demyelinating motor peripheral neuropathy in both lower limbs with a normal muscle biopsy. Seizures occur in more than half of the patients and electroencephalograms are always described as diffuse slowing.[19] Spastic paraplegia is a typical manifestation of argininemia, but this causes it to be easily misdiagnosed as other neurological diseases such as cerebral palsy, hereditary spastic paraplegia (HSP), or X-linked adrenoleukodystrophy.[10] Our patient also presented with the typical clinical features of spastic paraparesis at 10 years old. Based on these findings, in the absence of underlying risk factors for perinatal brain injury and the presence of unexplained progressive neurologic signs, clinicians might carefully consider a possible diagnosis of metabolic diseases because some of them – including argininemia – are potentially treatable.

Compared with patients with other urea cycle disorders, argininemia patients do not typically show significantly increased

blood ammonia, making diagnosis even more difficult (although in rare cases, higher blood ammonia levels can appear in the neonatal and early infancy periods).[20–22] Some patients have shown episodic hyperammonemia of differing degrees, but rarely of a life-threatening magnitude.[5,22] The blood ammonia of our patient was slightly elevated. Liver damage is a common complication of argininemia, including neonatal jaundice, hepatomegaly, cirrhosis, and hepatocellular carcinoma.[23–25] Although our patient had no hepatomegaly, he did present with mildly persistently elevated bilirubin, indicating cholestasis, at 3 years old, along with mildly elevated liver transaminase at 10 years old. These atypical lab test results are nevertheless easily neglected by clinicians. The reason for the positive urine occult blood test in our patient is not clear. We suspected that this might relate to the high level of L-arginine in serum. Delwing reported that arginine causes an oxidative imbalance in the renal tissues.[26] A positive urine occult blood has never been reported before in patients with argininemia.

4. Conclusion

We describe a Chinese patient with argininemia who exhibited a new phenotype of stunting, PGHD, progressive spasticity, peripheral neuropathy, cognitive lesions, epilepsy with atypical liver damage, and slight elevation of blood ammonia. This report should alert clinicians that the clinical picture of argininemia is strikingly uniform and can be easily misdiagnosed in children presenting with stunting and PGHD. Argininemia is a potentially treatable disease, especially in its early stages, so children presenting with stunting, self-selected low protein diet, progressive spastic paraplegia, peripheral neuropathy, and cognitive lesions, in the absence of evidence of other neurological disease, should be screened for argininemia.

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