DOI:10.4274/tnd.2020.97752
Turk J Neurol 2020;26:250-252

Case Report / Olgu Sunumu

A Rare Cause of Spasticity and Microcephaly: Argininemia

Spastisite ve Mikrosefalinin Nadir Bir Nedeni: Arjininemi

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Abstract

Argininemia is an autosomal recessive urea cycle disorder caused by the deficiency of arginase. Our first case presented with psychomotor retardation, difficulty of walking, and progressive tiptoeing. Laboratory investigations revealed mildly elevated hepatic enzymes and elevated plasma arginine concentration. Molecular genetic analysis was performed for suspected argininemia and a novel homozygous mutation c. 231C> A (p. S77R) was detected in the *ARG1* gene. The second patient was admitted because of poor head control when he was aged 6 months. Microcephaly was detected in his physical examination, and basic metabolic tests were studied. Elevated levels of plasma arginine and orotic acid in urine organic acid analysis were compatible with argininemia. A homozygous mutation c.703G> C (p. G235R) was detected in the *ARG1* gene and the diagnosis was confirmed. Argininemia is a rare cause of progressive spastic diplegia. Patients may be mistakenly diagnosed as having cerebral palsy. Microcephaly may be the initial clinical finding of the disorder.

Keywords: Arginase deficiency, microcephaly, spastic paraparesis, urea cycle defect

Öz

Arjininemi, arjinaz eksikliğinden kaynaklanan otozomal resesif, bir üre siklus bozukluğudur. İlk olgumuz psikomotor gerilik, yürümede zorluk ve progresif parmak uçlarında yürüme şikayetleri ile başvurdu. Laboratuvar incelemeleri ılımlı karaciğer enzim yüksekliği ve yükselmiş plazma arjinin konsantrasyonunu gösteriyordu. Arjininemi şüphesi ile moleküler genetik analiz yapıldı ve *ARG1* geninde yeni bir homozigot mutasyon c. 231C> A (p. S77R) tespit edildi. İkinci olgu, altı aylık iken başını dik tutamama nedeniyle başvurdu. Fizik muayenesinde mikrosefali saptandı ve temel metabolik testler çalışıldı. Yükselmiş plazma arjinin ve idrar organik asit analizinde orotik asit seviyelerinin artışı, arjininemi ile uyumlu idi. *ARG1* geninde homozigot mutasyon c.703G> C (p. G235R) tespit edildi ve tanı doğrulandı. Arjininemi progresif spastik diplejinin nadir bir nedenidir. Hastalar yanlışlıkla serebral palsi tanısı alabilirler. Mikrosefali hastalığın başlangıç klinik bulgusu olabilir.

Anahtar Kelimeler: Arjinaz eksikliği, mikrosefali, spastik paraparezi, üre siklus defekti

Introduction

Argininemia is a rare, autosomal recessive, inborn error of metabolism due to arginase deficiency. The estimated prevalence is 1/363,000-2,000,000 individuals. The difference of argininemia from other urea cycle defects is that hyperammonemic encephalopathy is rarely seen. It is a neurometabolic disorder presenting with progressive spastic diplegia caused by mutations in the *ARG1* gene (1).

The majority of patients present with progressive neurologic signs such as spastic paraparesis or plegia, failure to thrive, mental retardation, and seizures. Encephalopathy due to hyperamonemia, ataxia and athetosis, recurrent nonconvulsive status epilepticus, and liver failure are rarely defined clinical findings of the disorder (1,2,3,4). Low protein diet, lowering regimens of ammonia, and supportive care are the treatment methods of the disease (5). Arginase I mRNA

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Received/Geliş Tarihi: 17.09.2019 **Accepted/Kabul Tarihi:** 05.02.2020

therapy is a novel promising therapeutic approach to replace deficient protein (6).

Case Reports

Case 1

A 4-year-old male, the second child of a consanguineous Turkish couple, presented with psychomotor retardation, difficulty of walking, and progressive tiptoeing. He was born by spontaneous vaginal delivery with a weight of 3800 g after a 40-week gestation. There was no history of an acute encephalopathic event in the newborn period. He was referred to our hospital with the diagnosis of cerebral palsy.

His body weight was 12 kg (below the 3% percentile), height was 90 cm (below the 3% percentile) and head circumference was 48 cm (-2SD). A physical examination revealed increased tonus of lower extremities, tiptoeing, and psychomotor retardation.

In laboratory investigations, the aspartate aminotransferase level was 126 (normal: 0-34) IU/l, the alanine aminotransferase level was 153 (normal: 10-49) IU/l, the plasma arginine level was 1072 (normal: 38-98) nmol/ml, the ammonia level was 38.4 (normal: 16-60) µmol/l, and the urinary orotic acid level was 182 mmol/mol creatinine (normal: 0-11). Argininеemia was considered in this patient with these clinical and laboratory findings. The diagnosis was confirmed through molecular genetic analysis. A homozygous novel mutation c. 231C> A (p. S77R) was found in the *ARG1* gene.

A low-protein diet with essential amino acid supplementation and sodium benzoate (250 mg/kg/day) was started. Although the patient has moderate spasticity, he can walk without help and his intelligence is mildly impaired. Cranial magnetic resonance imaging (MRI) revealed no abnormal findings and he has not had any seizures or encephalopathy. Plasma arginine levels remained around 300 nmol/ml after treatment.

Case 2

A 6-month-old patient was admitted because of poor head control. He was born by caesarean section after 39 weeks of gestation with a weight of 3000 g and his head circumstance was 33 cm (3-10% percentile) at birth. He was the first child of a nonconsanguineous Turkish couple.

His body weight was 7.5 kg (25-50% percentile), his height was 70 cm (75-90% percentile) and head diameter was 41.2 cm (below the 3% percentile). Hypotonia and microcephaly were the major clinical findings of the patient.

In laboratory investigations, complete blood count, blood glucose, alanine aminotransferase, aspartate aminotransferase, and creatine kinase levels were within normal limits. TORCH serology, cranial MRI, thyroid function, and cytogenetic tests were also normal.

Basic metabolic tests were studied for inborn error of metabolism. The ammonia level was 28 µmol/l. Elevated plasma levels of arginine (840, range: 38-98 nmol/ml) and urinary orotic acid level (150 mmol/mol creatinine (range: 0-11) in organic acid analysis were compatible with argininemia.

A homozygous mutation c.703G> C (p. G235R) was detected in the *ARG1* gene. A low protein diet (1.5 g/kg/day) with essential amino acid supplementation and sodium benzoate (250 mg/kg/day) was started.

He had minimal spasticity in the lower limbs and could walk without any help when he was aged 18 months. His intelligence was normal compared with healthy children of a similar age. Plasma arginine levels remained around 200-300 nmol/ml during follow-up and his head circumference was 3-10% percentile. This patient is currently being followed at another metabolism center.

The clinical findings, mutation analysis, and motor and mental developments of the patients are shown in Table 1. These case reports were written after receiving informed consent from the families.

Discussion

The arginase is the final enzyme of the urea cycle and catalyzes the conversion of arginine to urea and ornithine (7). Carvalho et al. (5) reported 16 patients with argininemia, and 6/16 (37%) of the patients have microcephaly. Lower limb spasticity was the first neurologic manifestation in 12 patients. Three individuals had seizure as their first clinical sign and one patient presented with ataxic tremor of the upper limbs. Although microcephaly was detected in six patients, it was not described as the first symptom.

Episodes of irritability, feeding difficulties, and lethargy can be rarely seen in argininemia due to hyperammonemia (8). Hyperargininemia is more closely linked to neurologic damage than hyperammonemia in argininemia. The neuropathogenic mechanism of hyperargininemia is not clearly understood. Some metabolites of arginine such as guanidine compounds and elevated levels of nitric oxide were shown to damage the brain because of their neurotoxic effects (9).

Hyperargininemia is one of the few treatable causes of spastic paraparesis and can be confused with cerebral palsy. Jichlinski et al. (2) reported a case of an 11-year-old girl who presented with a diagnosis of cerebral palsy, seizure, and fatigue. Our first case presented with progressive spasticity, similar to this case, which was confused with cerebral palsy before the diagnosis.

Edwards et al. (10) reported that spasticity did not develop in a 6-year-old patient with argininemia who was diagnosed in a neonatal screening program. Zhang et al. (11) reported two

Table 1. The clinical findings, mutation analysis, motor and mental development of our patients

Current report	Ethnicity	Sex	Mutation	Clinical findings at diagnosis	Neurologic status
Case 1	Turkish	Male	c. 231C>A	Psychomotor retardation, difficulty of walking, and progressive tiptoeing	Moderate spasticity, he can walk without help and his intelligence is mildly impaired
Case 2	Turkish	Male	c. 703G>C	Microcephaly and hypotonia	Minimal spasticity and can walk without any help and intelligence is normal when he was aged 18 months

patients diagnosed through neonatal screening at the age of 13 days and 30 days who did not show obvious clinical features during the follow-up period. Although our first patient was diagnosed at age four years, he has moderate spasticity with minimal impairment of intelligence. The second patient has minimal spasticity and could walk without any help when he was aged 18 months. His intelligence is also normal. Neonatal screening program combined with genetic analysis is important for early diagnosis and treatment.

Diez-Fernandez et al. (12) reported 66 mutations and showed that the most common mutations were p. Thr134Ile, p. Gly235Arg, and p. Arg21* in Brazil, China, and Turkey, resepectively. We found a novel homozygous mutation c. 231C>A (p. S77R) in the first case and a common homozygous mutation c. 703G>C (p. G235R) in the second. Asrani et al. (6) demonstrated that arginase I mRNA treatment increased functional protein expression of *ARG1* and an increase in urea. It can be a novel promising therapeutic approach in Argininemia.

Argininemia should be considered in the differential diagnosis in the presence of progressive neurologic signs such as progressive spastic paraparesis/plegia, mental retardation, and epilepsy. Although microcephaly is a fairly frequent clinical finding of argininemia, rarely it can be the initial symptom and may require investigation for inborn error of metabolism.

Ethics

Informed Consent: Written consent was obtained from their parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.C., H.P., H.G., H.G.P., Concept: P.S.U., M.K., F.K., S.G., Design: P.S.U., M.K., F.K., S.K., Data Collection or Processing: P.S.U., A.K.B., S.G., Analysis or Interpretation: M.K., S.K., F.K., H.P., Literature Search: S.G., H.G., H.P., A.K.B., Writing: P.S.U., M.C., H.G.P., H.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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