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Case Report

A Case with Autism Spectrum Disorder and Concomitant Arginase Deficiency

Otizm Spektrum Bozukluğu ve Arjinaz Eksikliği Birlikteliği Olan Olgu

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by lack of social interaction, limited areas of interest, and repetitive behaviors. Comprehensive screening studies have shown that the prevalence of ASD is increasing. Arginase deficiency is an autosomal recessive metabolic disorder that affects the last step of the urea cycle. In this report, clinical features, neurological findings and genetic analysis results of an 11-year-old boy diagnosed with ASD have been discussed. Additionally, accompanying late diagnosed arginase deficiency has been also highlighted. In addition to the coexistence of ASD and metabolic diseases, the importance of early diagnosis and treatment in such cases has been emphasized.

Keywords: Arginase deficiency disorder, autism spectrum disorder, inborn errors of metabolism, neurodevelopmental disorders

ÖZ

Otizm spektrum bozukluğu (OSB), sosyal etkileşim eksikliği, sınırlı ilgi alanları ve tekrarlayan davranışlarla karakterize edilen bir nörogelişimsel bozukluktur. Kapsamlı tarama çalışmaları, OSB'nin prevalansının arttığını göstermektedir. Arginaz eksikliği, üre döngüsünün son basamağını etkileyen otozomal resesif geçişli bir metabolik hastalıktır. Bu makalede OSB tanısı alan 11 yaşındaki bir erkek çocuğun klinik özellikleri, nörolojik bulguları ve genetik analiz sonuçları tartışılmıştır. Ayrıca, geç tanı konulan arginaz eksikliğine de vurgu yapılmıştır. Otizm ile metabolik hastalıkların birlikte görülmesinin yanı sıra, bu tür olgularda erken tanı ve tedavinin önemi vurgulanmıştır.

Anahtar kelimeler: Arginaz eksikliği hastalığı, otizm spektrum bozukluğu, doğuştan metabolizma hataları, nörogelişimsel bozukluklar

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, along with restricted interests and repetitive behaviors[1]. ASD may coexist with inborn errors of metabolism (IEM). Increased awareness of both autism and hereditary metabolic diseases has heightened interest in their comorbidities. While the exact prevalence of autism in individuals with hereditary metabolic disorders is not precisely known, it is estimated to be around 2% in individuals with autism[2]. Among these, conditions such as phenylketonuria, histidinemia, creatine deficiency syndromes, adenylosuccinate lyase deficiency, disorders of purine metabolism, mitochondrial diseases, and urea cycle disorders have been identified. The co-occurrence of autism and hereditary metabolic diseases is often associated with dysmorphic features, ataxia, microcephaly, epilepsy, and intellectual disability (ID)[3].

Arginase 1 deficiency (ARG1-D) is a metabolic disorder caused by a defect in the ARG1 enzyme in the final step of the urea cycle, and it is inherited in an autosomal recessive pattern[4]. It is the least common urea cycle disorder, and severe hyperammonemia is not expected. The birth prevalence of arginase deficiency in the United States is recently estimated to be 1.1 cases per live birth[5]. ARG1-D, primarily in early childhood, can cause spasticity, seizures, developmental delay, recurrent vomiting, nausea, and ID, with elevated arginine responsible for neurotoxicity[6].

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In this case report, based on the literature data, we aim to highlight the co-occurrence of ASD with a neurometabolic disorder of arginase deficiency.

CASE REPORT

An 11-year-old male patient walking on tiptoes presented to the child psychiatry clinic with difficulties in establishing relationships with his peers, inability to form long sentences, and to eat solid foods.

Medical History

It was revealed that the patient was delivered without complications by caesarean section at full-term, with a birth weight of 4000 grams. Seventeen days after birth he was admitted to the pediatric ward for bronchopneumonia and received respiratory support in the intensive care unit for five days, followed by an 18-day observation in the pediatric ward.

Regarding dietary history, the patient experienced difficulties in swallowing solid foods. When he was given complementary foods, he started to vomit after consuming solid foods. At the age of two, the patient experienced febrile convulsions, and at the age of eight, he had atonic seizures, and received the diagnosis of epilepsy for which he was receiving daily doses of 26 mg/kg levetiracetam.

Developmental Stages

Until the age of two, the patient was breastfed, achieved head control at two months, sat unsupported at eight months, walked, and started speaking single words when he was two years old. It was noted that the patient began walking on tiptoes before the age of two.

Family History

His high school graduate 43-year-old mother was a physically and mentally healthy hosewife. His high school graduate 44-year-old physically and mentally healthy father was engaged in real estate transactions to support the family. The patient who was the second child of the family had a healthy 16-year-old sister. There was no consanguinity between the parents. However there was motor and mental developmental delay in the father's cousins.

Physical Findings

The patient weighed 21 kg [-3.3 standard deviation score (SDS)], with a height of 138 cm (-0.9 SDS), beak nose, retrognathia, slender-long trunk, and restricted dorsiflexion of both feet. Neurologically, there was hyperlaxity in the upper extremities, spastic diplegia, with deep tendon reflexes being normoactive in the upper and hyperactive in the lower extremities. Muscle strength was evaluated as 5/5 in the upper extremities. The patient demonstrated a cross-stepping gait.

Psychiatric Examination

The patient's overall appearance indicated that he was younger than his actual age, and his self-care was age-appropriate. He was conscious, but there was a noticeable lag in perception and judgment compared to his peers. Reduced eye contact, not responding when called, using single words when talking, the presence of stereotypical behaviors such as wing-flapping tremors, echolalia, and engaging in repetitive play were observed. The Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version-Turkish Adaptation were administered to the patient. The Autism Behavior Checklist, filled out by parents, yielded a score of 52. Following the psychiatric examination, family interviews, and psychometric measurements, the diagnosis of ASD was made based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria[1].

Due to dysmorphic findings observed during the physical and neurological examination, the patient was referred to the pediatric health clinic.

Laboratory Tests

Laboratory investigations revealed elevated levels of aspartate aminotransferase (60 U/L), alanine aminotransferase (109 U/L, and ammonia (158 µmol/L). In consideration of these results, the patient was evaluated by a physician specialized in pediatric metabolism disorders. The metabolic laboratory examination revealed significantly high levels of plasma arginine (794 µmmol/L; normal range: 45-125 µmmol/L), and arginine level in a dried blood spot measured by tandem mass spectrometry was 338 µmmol/L (normal range: 10-130 µmmol/L).

Molecular Analysis

The Sophia Clinical Exome Panel, consisting of 4490 genes, was applied to the patient. The data obtained were analyzed using the Sophia-DDM-v4 program. A homozygous missense mutation c.703G>A (p.Gly235Arg) was identified in the *ARG1 gene* (NM_000045.3). This identified alteration was a pathogenic mutation previously reported in the literature[7]. Individuals carrying the G235A alteration have been shown to

lack arginase activity[7]. Targeted mutation analysis was performed on the parents of the patient, revealing that both parents carried the c.703G>A (p.Gly235Arg) mutation in a heterozygous state.

In addition, chromosomal microarray analysis was performed using Illumina Infinium Asian Screening Array-24 v1.0 kit. Data was analyzed with NxClinical program. The result was evaluated as normal.

Considering the patient's medical history, examination, and laboratory findings, arginase deficiency was suspected. The diagnosis was confirmed through molecular analysis. As a treatment, the patient's protein intake was restricted, and sodium benzoate therapy was initiated. According to DSM-5 diagnostic criteria, the patient was diagnosed with ASD developed on the basis of arginase deficiency, with a severity level of 3. In the initial evaluation, the Childhood Autism Rating Scale (CARS) score was 39, indicating severe autism. The patient was referred to a special education and rehabilitation program. After 6 months of special education and rehabilitation, and treatment for arginase deficiency, the case was re-evaluated. According to DSM-5, he received the diagnosis of ASD developed on the basis of arginase deficiency with a severity level of 2, and CARS score of 32.5, indicating mild to moderate autism. Written informed consent was obtained from the patient's parents for the publication of this case.

DISCUSSION

Arginase deficiency is a neurometabolic disorder inherited in an autosomal recessive pattern, manifesting as progressive spastic diplegia. The estimated prevalence is approximately 1 in 363,000 to 2,000,000 live births. Arginase deficiency rarely presents in the neonatal period, and most patients are typically identified as normal in early stages of their lives. The significant feature that distinguishes arginase deficiency from other urea cycle disorders is that it does not present with hyperammonemia, especially in the newborns and infants[5,6]. Initial symptoms usually manifest between 2 and 4 years of age and include stumbling, falling, and delays in growth and development. If not diagnosed, and treated at an early stage, patients may experience progressive spastic diplegia, leading to a gradual loss of developmental milestones. The most prominent symptoms include spastic paraparesis or paraplegia with less impact on the upper extremities, increased deep tendon reflexes, walking on tiptoes, behavioral problems, ID, and seizures. Some patients also exhibit symptoms such as nausea, loss of appetite, and vomiting attacks[6]. Although elevated plasma arginine levels are the most critical diagnostic criterion, elevated liver function test results, decreased blood urea nitrogen, increased plasma citrulline levels, and orotic acid excretion in urine are supportive diagnostic findings. It should be noted that while hyperammonemia is not expected in newborns and infants, it may be observed in the late-childhood stage, particularly during catabolic processes[5,6,8]. Treatment typically involves a diet restricted in protein, supplementation of essential amino acids, and the use of other alternative treatment modalities using sodium benzoate and sodium phenylbutyrate, to remove nitrogen waste. The benefits of treatment have been demonstrated in overcoming behavioral problems and reducing seizures[8].

Various studies have previously investigated the prevalence of neurodevelopmental disorders in individuals with IEM. The best-known inborn metabolic disorders include phenylketonuria, classical homocystinuria, Sanfilippo disease, urea cycle disorders, creatine deficiency syndromes, and purine metabolic pathway disorders[2,9-13].

In a study conducted by Spilioti et al.[9] in Crete, IEM were identified in 5 out of 187 patients with ASD. A study from Turkey, evaluating 237 patients with ASD, detected 6 cases with IEM[11]. In another study conducted in our country, 22 patients with both ASD and IEM were examined in a tertiary care hospital, and none of them were found to have arginase deficiency[10]. In this case report we present the rare coexistence of ASD, with arginase deficiency which was not detected even in large-scale studies.

In the study by Kiykim et al.[13], metabolic diseases were detected in 9 out of 300 patients with ASD, and argininemia was identified in only one case. Although arginase deficiency was not found in this patient, the potential role of elevated arginine in autism was emphasized. In a case from Bahrain, a 14-year-old patient with a diagnosis of ASD was found to have arginase deficiency, and it was reported that there was no significant improvement in ASD scores after treatment[14]. In our patient, a decrease in the severity scores of ASD was observed after treatment. This improvement in indicators of ASD severity over a short period, such as six months, suggests that the likelihood of benefiting from treatment increases, especially when the diagnosis is made at an early stage of the disease.

Bin Sawad et al.[15] systematically reviewed case reports of 157 patients diagnosed with arginase deficiency. Motor

impairments, ID, and seizures, including spasticity, were reported in more than half of the cases examined. Our case also exhibited all of these manifestations. The average age at diagnosis was determined to be 6.4 years, and our case could be considered a late diagnosis compared to this age criterion. Clinical improvement after treatment was reported in only 26% of patients. In our patient, clinical improvement was observed after only 6 months of treatment.

Schiff et al.[12] identified only 2 patients with suspected metabolic disorders among 274 non-syndromic ASD patients. They emphasized the importance of metabolic screening in individuals with dismorphic features and additional neurological symptoms rather than in patients with non-syndromic ID. In our case, spastic diplegia was a prominent non-ASD physical examination finding which underscores the significance of a thorough systemic examination in individuals with ASD.

In cases diagnosed with ASD, especially when there are dysmorphic features and accompanying neurological signs, it is crucial to refer individuals for metabolic screening to the departments of pediatrics and pediatric metabolism. Early diagnosis, coupled with medical intervention, leads to life-saving outcomes serves as a cornerstone in preventing autism and ID, and enhances the effectiveness of special education, contributing positively to the quality of life of the patients.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the patient for the publication of details of the medical case.

Author Contributions

Concept: B.G.Ö., Design: R.E., B.C.Ö., B.G.Ö., Data Collection and Processing: E.G., Z.M.Y., Analysis and Interpretation: E.G., Z.M.Y., Literature Search: R.E., B.C.Ö., Writing: R.E., B.C.Ö., E.G., Z.M.Y., B.G.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

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