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A Rare Genetic Disorder Presenting with Neuropsychiatric Involvement and Drug-Resistant Epilepsy: The First Adult Patient with Adenylosuccinate Lyase Deficiency in Türkiye

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Adenylosuccinate lyase (ADSL) deficiency is a rare autosomal recessive metabolic disorder of the purine biosynthetic pathway caused by mutations in the *ADSL* gene, located on chromosome 22q13.1-q13.2.1 (1). The clinical presentation associated with ADSL deficiency can be extremely heterogeneous and is classified into three main groups based on age of onset and clinical severity (neonatal, type I, type II) (2). Epilepsy is a core feature of the disease, characterized by polymorphic and often drug-resistant seizures. Patients typically display common electroencephalographic features and evolutionary trajectories (3). Herein, we present the first adult patient with genetically confirmed ADSL deficiency in our country to raise awareness of this rare disease.

This 38-year-old female patient, born to consanguineous Turkish parents, was delivered at term. Her prenatal and perinatal histories were unremarkable. At 4 to 5 months of age, her mother observed hypotonia, delay in motor and social developmental milestones and autistic behaviors including midline stereotypic motor activities. At around 11 months of age, a "Rett-like" syndrome was diagnosed. Later, at the age of 6 years, drug-resistant epilepsy (DRE) developed characterized by myoclonic and generalized tonic-clonic seizures that could not be controlled with valproate and lamotrigine. In conjunction with DRE, the patient developed severe motor and intellectual disability, ataxia, tremor-like movements of the head and extremities and spastic quadriparesis. Electroencephalogram (EEG) revealed a disorganized background with generalized spike-wave discharges predominantly on the frontocentral regions along with multi-focal epileptiform abnormalities on the frontal regions. Cranial MRI at 3 Tesla with thin slices showed diffuse cerebral and cerebellar atrophy, thinning of the corpus callosum, and white matter abnormalities. Whole exome sequencing (WES) identified a pathogenic homozygous mutation in the *ADSL* gene: Chr22:40760969, NM_000026.3:c. 1277G >A, p. (Arg426 His). Segregation analysis demonstrated compound heterozygous inheritance, as each parent was found to be a carrier of.

Highlights

- **Adenylosuccinate lyase (ADSL) deficiency is a rare metabolic disorder**
- **Epilepsy is a core feature of the disease.**
- **The first adult patient with genetically confirmed ADSL deficiency was presented.**

Adenylosuccinate lyase deficiency presents variable phenotypic expression, the severity of which may be partially attributed to the residual activity of the mutant protein. Type I is the most common form of this metabolic disorder and is characterized by a severe neuromotor developmental disorder beginning in the first months of life, accompanied by intellectual disability, autism, axial hypotonia, hypertonia in the extremities, dystonia, and ataxia. Epilepsy is observed in nearly all patients with this rare hereditary metabolic disorder, which has now been identified in our country and currently lacks an effective treatment.

The seizures are often drug-resistant and interfere with daily living activities. They may be focal or generalized in type, and may present as epileptic spasms or status epilepticus.

In milder forms, valproate, levetiracetam, and lamotrigine have been reported to be effective, while ketogenic diet, D-ribose, and S-adenosyl-L-methionine have been suggested as adjunctive treatments in drug-resistant cases (4).

In patients with psychomotor delay, epilepsy, prominent autistic features, and pyramidal-extrapyramidal signs, ADSL deficiency might be considered in the differential diagnosis of epileptic encephalopathies.

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In this rare condition, where only symptomatic treatments are currently available, the ability to achieve an advanced etiological diagnosis through next-generation sequencing techniques and to identify carriers is within families is of significant clinical importance. Given the high prevalence of consanguineous marriages in our country, accurate genetic diagnosis and identification of carriers should not be overlooked for disorders like ADSL deficiency, which pose significant challenges for both affected individuals and their families.

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