Identification of A Novel Hemizygous *SLC16A2* Nonsense Mutation in Allen-Herndon-Dudley Syndrome

Allen-Herndon-Dudley Sendromunda yeni Bir Hemizigot SLC16A2 nonsense mutasyonu

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ABSTRACT

Allan-Herndon-Dudley syndrome (AHDS) is a rare X-linked inherited disease that prevents absorption of thyroid hormone and causes axial hypotonia, weakness, and severe intellectual disability. The syndrome is caused by mutations in the *SLC16A2* (known as *MCT8*) gene. This gene encodes the brain transporter of thyroid hormones. Deficiency of MCT8 leads to a lack of T3 entry in the brain, which causes central hypothyroidism. We described a boy who manifested congenital hypotonia, severe developmental delay, mental retardation, muscle weakness, and dystonia. He was diagnosed with AHDS which details the clinical and biochemical findings. A novel pathogenic nonsense (c.25G>T;p.E9X) mutation in the *SLC16A2* gene was identified by direct sequencing. This case can expand the mutational spectrum of *SLC16A2* gene mutations and support the clinical features of AHDS.

Key words: MCT 8 defficiency, Hypotonia, *SLC16A2* Gene, Thyroid hormone abnormality.

ÖZET

Allan-Herndon-Dudley sendromu (AHDS), tiroid hormonunun emilimini önleyen ve aksiyal hipotoni, güçsüzlük ve ciddi zihinsel yetersizliğe yol açan, X'e bağlı, nadir görülen bir kalıtsal hastalıktır. SLC16A2 (MCT8 olarak bilinir) genindeki mutasyonlar hastalığa neden olmaktadır. Bu gen, tiroid hormonlarının beyine transferini sağlayan bir proteini kodlar. MCT8 eksikliği, beyinde merkezi hipotiroidizme neden olan T3 girişi eksikliğine yol açar. Doğuştan hipotoni, ciddi gelişim geriliği, zeka geriliği, kas güçsüzlüğü ve distoni ile kendini gösteren kliniğe sahip bir erkek çocuğu tanımladık. AHDS teşhisi kondu, klinik ve biyokimyasal bulguları detaylandırıldı. SLC16A2 genindeki yeni bir patojenik anlamsız (c.25G>T;p.E9X) mutasyon, SLC16A2 gen dizi analizi ile tanımlandı. Bu vaka, SLC16A2 gen mutasyonlarının mutasyonel spektrumunu genişletebilir ve AHDS'nin klinik özelliklerini destekleyebilir.

Anahtar Kelimeler: MCT 8 eksikliği, Hipotoni, SLC16A2 Geni, Tiroid hormon anormalliği.

INTRODUCTION

Thyroid hormone is essential for the metabolism, development, and thermogenesis of the brain and other tissues. T3 (triiodothyronine) requirement of the brain is obtained from T4 (thyroxine) by neighboring tissues in a paracrine way (1). T3 is an active form of thyroid hormone and binds to nuclear receptors changing transcription starting complex associated protein and stimulates or suppresses thyroid hormone linked genes. Monocarboxylase transferase (MCT) 8 plays a role in thyroid hormone transport in thyroid tissue. MCT8 defficiency causes high T3, low-normal T4 and high-normal TSH (thyrotropin) (2). Allan-Herndon- Dudley syndrome (AHDS) is caused by a mutation in the *SLC16A2* (also known as *MCT8*) gene by preventing transportation of thyroid hormone produced by the thyroid gland into the brain (3). This syndrome is characterized by severe cognitive delay, hypotonia, generalized muscle weakness, spastic quadriplegia, joint contractures and dystonic and/or athetoid movement (4). Here we present a boy with AHDS diagnosed by a novel pathogenic *SLC16A2*

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(c.25G>T; p.E9X) gene mutation with involuntary movements and developmental delay.

CASE REPORT

A 4-year-old boy was born from a non-consanguineous couple with a birth weight of 3420 gr, 52 cm birth length presented with abnormal dystonic posture. He was born by normal spontaneous vaginal delivery at term. The APGAR score was 9 and 10 points in the first and fifth minutes, respectively. His birth weight, length and head circumference were normal. The thyroid function tests had not been measured in that period. Any thyroid hormone dysfunction was not detected during the neonatal screening. He had dystonia in the upper and lower limbs during awake periods. His family history showed that his uncle (his mother's brother) was normal until 9 months of age and developed severe convulsions afterwards. He died because of a pulmonary infection at 1.5 years-old. The weight was 14 kg (7% percentile), height was 90 cm (1% percentile) and the height standard deviation -3SD. He had a long face, myopathic facial features with an open mouth appearance, a long philtrum, big and long ears, nystagmus, pectus excavatum, and hypotonia. He was unable to control his head. He had also dystonic posture backwards and myoclonic jerks with noise. His deep tendon reflexes were hypoactive. TSH was 5,1 mU/L (N: 0,7–4,9 mU/L), free T4 was 0.66 ng/dl (N: 0,8–2,2ng/dl), and free T3 was 7.02 pg/ml (N: 2,4–4,2 pg/ml). Laboratory tests including liver and renal function, lactic acid, creatine kinase, and ammonia were also normal. Further tests, including an electroencephalogram, thyroid ultrasonography, karyotype analysis by G-banding, chromosomal microarray, spinal muscular atrophy, and congenital muscular dystrophy, revealed no abnormalities. AHDS has been considered by neurologic and endocrinologic examinations. Direct sequencing of the *SLC16A2* gene was performed that revealed a novel pathogenic (c.25G>T;p.E9X) hemizygote mutation. This is a nonsense mutation of the *SLC16A2* gene (p.E9X), resulting in premature termination of protein synthesis. Using Mutation Taster, the variant was predicted as disease causing. The mutation was not found in the dbSNP, 1000G, HGMD, or ExAC databases. The segration analysis showed that the father was negative, and the mother was a heterozygote mutant of *SLC16A2* gene. Cerebral magnetic resonance imaging (MRI) was performed when he was 4-year-old and it revealed a delay in myelination and a pineal cyst. The other MRI revealed brain atrophy, an increase in peripheric cerebrospinal fluid (CSF) dimension and a pineal cyst (Figure 1). Informed consent was obtained from the parents of the proband.

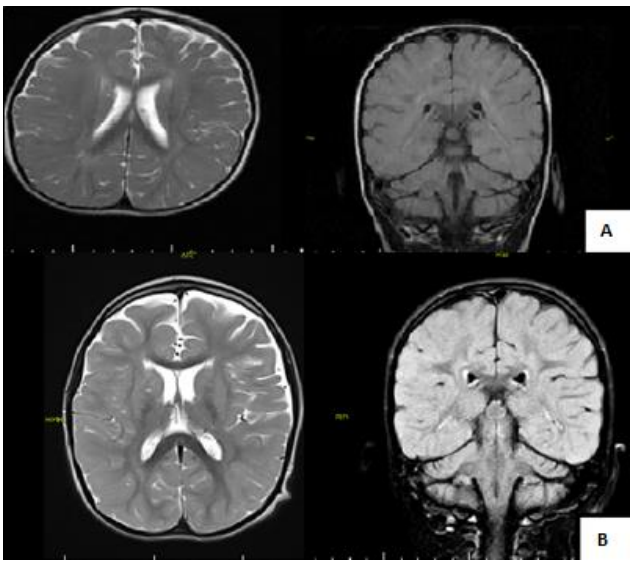

Figure 1. The features of MRI at different ages. **1A.** Demyeleiation, pineal cyst at 4 years of age. **1B.** Cerebral atrophy, pineal cyst at 7 years of age.

DISCUSSION

We report a four-year-old boy with an increased fT3 and TSH; a low freeT4 serum level and genetically confirmed the AHDS diagnosis. The findings of the AHDS are central hypotonia, inability to control the head, peripheric hypotonia at the start of evolving

hypertonia, and spasticity at later stages (5). The clinical findings in our case were similar to those reported in other patients before. Our patient presented with congenital hypotonia, muscle weakness, movement disorders, mental retardation and dystonia (6). The patients' thyroid hormone profile is fT4 and total-T4 levels are low or low-normal, fT3 levels are frequently very low, and TSH levels are frequently high-normal (7,8). The thyroid profile in our patient is consistent with the literature. More than 80 different mutations of *SLC16A2* gene have been described from over 100 families to date (9). The identified mutations of the *SLC16A2* gene include causing splice site mutations, deletions or insertions of one or more codons, nonsense mutations causing a premature truncation of the MCT8 protein and missense mutations leading to 1-amino-acid substitutions (10). We detected a novel nonsense mutation (c.25G>T;p.E9X) of the *SLC16A2* gene in our patient. The larger deletions, frame-shift mutations and nonsense mutations are deleterious for MCT8 function (11). We suggest that this novel nonsense mutation leads to the stop codon resulting from insufficient production of MCT8 protein. AHDS shows a clinically heterogeneous spectrum according to the type of mutation and its effect on protein synthesis (12). Our patient fits the most severe phenotype with both the mutation type and the clinical findings. Delayed myelination and white matter changes may be seen on MRI with MCT8 defficiency (13-15). The cerebral MRI showed delayed myelination, a pineal cyst and cerebral atrophy in our patient. The findings can help the clinician diagnose AHDS using a specific genetic analysis of the *SLC16A2* gene (16-17). In summary, we describe a novel nonsense *SLC16A2* gene (c.25G>T;p.E9X) mutation identified in a boy with severe neurological impairment and high serum T3 concentration. We suggested that the diagnosis of AHDS be suspected in the presence of an abnormal thyroid profile characterized by elevated T3, low-normal to low free T4 and normal to increased TSH. The routine measurement of thyroid function tests in children with developmental delay and hypotonia may prevent delay in the diagnosis of AHDS. Adding new cases to the literature is expected to increase our knowledge about the prevalence of the disease, clinical symptoms, and genotype-phenotype correlation.

CONCLUSION

Through this case report, we also demonstrate the importance of excluding AHDS by investigating the thyroid hormone status in an infant boy with hypotonia and severe developmental delay.

Informed Consent: Informed consent was taken from the patient.

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

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