Allan-Herndon-Dudley Syndrome 환아에서 발견된 novel c.826G>A Mutation

A Novel c.826G>A Mutation in a Boy with Allan-Herndon-Dudley Syndrome: Clinical Significance of Thyroid Function Tests in Developmental Delay of Unknown Origin

Allan-Herndon-Dudley syndrome (AHDS) is an X-linked intellectual disability caused by monocarboxylate transporter 8 (MCT8) deficiency. AHDS manifests in global developmental delay, axial hypotonia, quadriplegia, movement disorders in male patients, and most of them show the delayed or hypomyelination on brain magnetic resonance images. Typically, Triiodothyronine (T3) levels are markedly elevated, thyroid stimulating hormone (TSH) levels are normal or elevated, and free thyroxine (T4) levels are normal or decreased. In AHDS patients, early neurological manifestations are easily mistaken as cerebral palsy with unknown origin. Here, we present a novel c.826G>A mutation in a boy with severe axial hypotonia, limb dystonia and developmental delay. Thyroid function test including TSH, T3, and free T4 levels was the important clue for the diagnosis of AHDS of the patient.

Key Words: Allan-Herndon-Dudley Syndrome, monocarboxylate transporter 8 (MCT8), neurodevelopmental delay, movement disorders, thyroid hormone, transporters

Introduction

Allan-Herndon-Dudley syndrome (AHDS) is a rare X-linked disorder characterized by neurological abnormalities, developmental delay, and altered thyroid function in male patients. Since the era of magnetic resonance images (MRI), a delay in white matter myelination has become a signature finding in the majority of patients with AHDS.

In 2004, the causative gene monocarboxylate transporter 8 (MCT8) located on chromosome Xq13.2 was discovered, and, since then, more than 79 mutations have been reported globally. Affected patients present with severe developmental delays, such as inability to head control, global or axial (truncal) hypotonia, dystonia and a variety of movement disorders, quadriplegia, spasticity, and muscle weakness. Growth failure, seizures, gaze abnormalities, and recurrent respiratory infections are frequently associated with AHDS. For the...
diagnosis of AHDS, thyroid function test including thyroid stimulating hormone (TSH), triiodothyronine (T3), and free thyroxine (T4) levels are important.

In the present study, we report a novel c.826G>A mutation in a boy whose main manifestations were severe hypotonia and developmental delay.

Case report

A 7-month-old male infant was referred to our pediatric department for delayed development and failure of weight gain. His parents noticed his motor delay at 6 months of age. At the first visit, he started to roll over, but was not able to control his head, sit without assistance, or grasp small objects. He uttered simple vowel sounds (cooing), and responded to his mother’s voice. Eye contact and social smile were present. His weight was 7.4 kg (percentiles 3–5), his height was 69 cm (percentiles 10–25), and head circumference was 41.6 cm (percentiles 5–10).

The boy was born at 38 weeks of gestation by uneventful vaginal delivery with a birth weight of 2.6 kg (percentile 3). He is an only child of a 42-year-old father in good health and a 42-year-old mother with intellectual difficulties. He had no severe medical problems until his first visit, and no family history of hereditary neurological diseases.

On physical examination, he seemed weak and apathetic. A myopathic face, positional plagiocephaly, strabismus of the left eye, high arched palate, and wasted muscles were noted. The respiratory sound of the patient’s breathing was noisy. At a supine position, his posture was curved and easily became dystonic when stimulated. His hands were persistently fisted, and his ankles were contracted. His upper extremities seemed hypertonic, but his traction response showed marked truncal hypotonia (Fig. 1A–C). Tendon reflexes were increased.

1. Laboratory findings and Developmental test

The Korean Infant and Children Developmental Test showed a low total developmental quotient (DQ) of 38 (normal range: 80–120), a total developmental age (DA) corresponding to 3 months, and a profound delay in all areas of development, resulting in a global developmental delay. Laboratory findings were within normal ranges: white blood cell count, 11,300/mm$^3$; pH, 7.44; base excess, -2.2 mmol/L; hemoglobin, 12.2 g/dL; platelet count, 319/mm$^3$; total protein, 6.5 g/dL; albumin, 4.8 g/dL; alanine transaminase, 45 U/L; aspartate transaminase, 41 U/L; total bilirubin, 0.4 mg/dL; calcium, 10.2 mg/dL; phosphorus, 5.6 mg/dL; creatine kinase, 141 U/L; sodium, 136 mEq/L; potassium, 4.3 mEq/L; ammonia, 50 µmol/L; lactate, 1.4 mmol/L; ketone, 159.4 µmol/L; and glucose, 101 mg/dL. Tandem mass screening, serum amino-acid evaluations, and urine organic acids test

Fig. 1. (A) The patient showed plagiocephaly, myopathy, delayed head control, and strabismus. (B) The general posture of the patient: dystonic posture of the limbs, fisted hands, and ankle contractures. (C) A traction test showed severe head lag sign. (D) T2 axial fluid-attenuated inversion recovery (FLAIR) MRI images, performed at the age of 7 months, revealed diffuse hypomyelination and ventriculomegaly.
results were nonspecific. However, a thyroid function test (TFT) showed increased T3 levels (3.1 ng/mL; reference 0.75–2.6), normal TSH levels (4.1 µIU/mL; reference 0.7–6.4), and reduced free T4 levels (0.64 ng/dL; reference: 0.9–2.6). The patient’s chromosomal analysis revealed a normal karyotype (46, XY). Results from a radiologic skeletal survey and an electroencephalogram were normal. Brain MRI, performed at the age of 7 months, showed equivocal ventriculomegaly and delayed myelination considering the boy’s age (Fig. 1D).

2. Genetic Analysis
As the boy’s neurologic abnormalities, delayed myelination visible in brain MRI, and altered TFT results suggested AHDS, we performed further genetic analyses. Direct sequencing for the MCT8 (also known as SLC16A2) gene showed a hemizygous missense mutation at c.826G>A (p.Gly276 Arg) (Fig. 2). In vitro assay, the functional consequences of the mutation were not analysed. But p.Gly276 Arg is highly conserved across various species (mutationtaster.org). This mutation is not present in dbSNP (https://www.ncbi.nlm.nih.gov/SNP/), 1000 Genomes (http://browser.1000genomes.org), or ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/). This variant was previously predicted to alter protein function by in silico analysis using SIFT (http://sift.jcvi.org) and polyphen-2 (http://genetics.bwh.harvard.edu/pph2/). Subsequent genetic analyses of his parents revealed that his mother was a carrier of this mutation.

Discussion
The thyroid hormone plays a fundamental role in normal neurological development and maintenance. Both hypothyroid and hyperthyroid states can impair early childhood neurodevelopment and somatic growth and thus lead to cognitive, movement, and neuromuscular disorders and failure of weight gain.

AHDS is a genetic thyroid metabolism disorder resulting from a MCT8 mutation. MCT8 is a specific thyroid hormone transporter with a preferential specificity to T3. MCT8 is mainly expressed in the brain and critically affected by reduced levels or the absence of T3, which induces the differentiation of glial cells. As a result, laboratory results for AHDS show increased serum T3 levels, normal to increased TSH levels, and normal to decreased free T4 levels. Overt hyperthyroid conditions are rare, but failure of weight gain is thought to be caused by a hyperthyroid metabolic condition. The prevalence of the MCT8 mutation as the cause of X-linked mental retardation is uncertain. Until now, more than 50 cases of genetic mutations have been reported worldwide (http://www.hgmd.org).

Even though the neurological features of AHDS are characteristic, early expressed truncal hypotonia, quadriplegia, and hypertonic postures may lead to the patient receiving rehabilitation treatment directed at ameliorating spasticity, with usually suboptimal effects. Recently, redefinition of the clinical features of AHDS suggested that early presented hypertonic postures were mainly caused by dystonia, and that true spasticity gradually presents as patients aged.

Brain MRI of patients with AHDS reveals a range of manifestations from hypomyelination to markedly delayed myelination. Neurological abnormalities and hypomyelination patterns characteristic of AHDS are easily confused with a variety of neurodegenerative leukodystrophies such as Pelizaeus-Merzbacher disease, metachromatic leukodystrophy, X-linked adrenoleukodystrophy, and other rare white matter diseases. On the contrary PLP1–related Pelizaeus–Merzbacher disease, myelination finally complete in older AHDS patients. Although
delayed myelination is regarded as a universal finding in AHDS, normal myelination patterns have been reported in patients with MCT8 mutations. It should therefore be pointed out that AHDS can occur in patients with typical clinical profiles and normal brain myelination\(^\text{20}\). Muscle weakness is frequently associated with AHDS, which may be caused by both hypo- and hyperthyroid states. As tendon reflexes can be increased or decreased, and the patient’s face seems myopathic, various neuromuscular disorders should be ruled out in the differential diagnosis. However, before electromyography, genetic studies, or even biopsies for neuromuscular disorders are conducted, a simple thyroid hormone assay evaluation will provide an indication for the diagnosis of AHDS\(^\text{8}\).

In the present case, the main problem for the correct diagnosis of AHDS was the severe developmental delay in all areas and easily detectable hypotonic and dystonic postures. Although the patient showed severe axial hypotonia, his fisted hands and extremities seemed hypertonic. Brain MRI findings showing delayed myelination and ventriculomegaly can be found in various neurological conditions; therefore, they do not indicate a particular brain disorder. In addition, tendon reflexes were increased, and extensive laboratory test results for indications of neurological abnormalities were not significant. In such cases, the most common misdiagnosis would be cerebral palsy of unknown origin. However, the patient’s thyroid hormone test (increased T3, normal TSH, decreased free T4 levels) indicated an altered thyroid hormone metabolism. The combination of a global developmental delay, severe truncal hypotonia, dystonic limb position, and TFT abnormalities suggested the diagnosis of AHDS, and following an MCT8 gene analysis, we found a hemizygous missense mutation at c.826G>A (p.Gly276 Arg), which has not been reported before.

In this patient, the mutation originated from his mother. The mothers of affected boys are usually carriers with normal function, but his mother showed intellectual disabilities. Intellectual disabilities in female carrier have been reported in rare cases\(^\text{4}\). At this time, the reason of her intellectual disabilities is uncertain. To further determine the mother’s state of carrier or patient, methylation tests would be helpful.

The therapeutic options for conditions as the one described here are limited. When previous patients were treated with levothyroxine (L-T4) or with L-T4 combined with propylthiouracil, normalization of thyroid function and weight gain have been reported, but neurological outcomes did not improve\(^\text{9}\). The biologically active T3 metabolite, 3,3',5-triiodothyroacetic acid (TRIAC), is a potential therapeutic option because it is transported into brain cells by other transporters and has greater affinity to the thyroid hormone receptors alpha and beta than T4. However, TRIAC administration in MCT8 KO mice is not sufficient to increase TRIAC levels, but rather causes a state of brain hypothyroidism with reduced T3 concentrations\(^\text{10}\).

In Korea, two heterozygous mutations (p.I114N and p.A224V) have been reported in patients with psychomotor retardation, truncal hypotonia and spastic paraplegia by Kim et al\(^\text{11}\). They reported that serum T4 normalized 1 year after levothyroxine administration, but developmental milestones and poor weight gain did not improve\(^\text{10}\).

In the present study, we described a novel c.826GA mutation in AHDS infant with distinguishing photos of the patient. Usually, T3 levels are not tested in routine newborn screening. We suggest that tests of thyroid profile including T3 would be an essential clue to the diagnosis of ADHD in patients with unknown dystonia and axial hypotonia.

요약

Allan-Herndon-Dudley syndrome (AHDS)은 monocarboxylate transporter 8 (MCT8)의 결핍으로 인하여 발생하는 X-연관성 지적지연 질환이다. AHDS은 전반적 발달지연, 신체 중심축의 저긴장증, 사지마비, 운동이상 등을 주 증상으로 나타내며 대부분의 경우 더 자체공명영상검사에서 지연된 수초화 또는 저수초화를 보인다. 검사소견에서 전형적으로 Triiodothyronine (T3)의 현저한 증가, thyroid stimulating hormone (TSH)의 정상 또는 증가, free thyroxine (T4)의 정상 또는 감소 소견을 보인다. AHDS 환자들에서 관찰되는 초기 신경학적 이상들은 혼히 원인불명의 사지마비이나 저기관장 증상을 나타내는 뇌질환으로 오인하기 쉽다. 본 저자는 심한 중심축 저기관장증, 사지의 근간장이상, 그리고 발달연차를 주소로 내원한 남아에서 새로 발견된 c.826GA 돌연변이로 인한 AHDS 1례를 보고하고자 한다. T3, TSH, freeT4를 포함하는 갑상선호르몬 검사의 이상환자 AHDS로 진단하는 것에 중요한 단서가 되었다.

References

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