Case Report

Thyroid Hormone Transporter Defect: Allan Herndon Dudley Syndrome, Masquerading as Dyskinetic Cerebral Palsy

Vyakuntaraju Kammasandra Gowda, Priya Gupta, Sanjay K. Shivappa¹, Naveen Benakappa¹

Department of Pediatric Neurology, ¹Department of Pediatric Medicine, Indira Gandhi Institute of Child Health, Bangalore, India

Allan Herndon Dudley syndrome (AHDS) is a rare X-linked recessive disorder due to mutation in the SLC16A2 gene, which encodes a thyroid hormone (TH) transporter that facilitates the movement of TH across the neurons. Mutation in this gene leads to a lack of T3 and T4 entry in the brain, which causes central hypothyroidism and dysthyroidism in the peripheral tissue. We report a child, a 21-month-old boy, who presented with developmental delay and stiffness. The child had facial dysmorphism with dystonia. MRI of the brain was normal. Thyroid profile showed low free T4, and normal TSH but high free T3. Hence, AHDS was suspected and was confirmed by targeted next-generation testing and Sanger sequencing.

**Key words:** Allan Herndon Dudley syndrome, central hypothyroidism, dystonia, SLC16A2

**Abstract**

Allan Herndon Dudley syndrome (AHDS) is a rare X-linked recessive disorder due to mutation in the SLC16A2 gene, which encodes a thyroid hormone (TH) transporter that facilitates the movement of TH across the neurons. Mutation in this gene leads to a lack of T3 and T4 entry in the brain, which causes central hypothyroidism and dysthyroidism in the peripheral tissue. We report a child, a 21-month-old boy, who presented with developmental delay and stiffness. The child had facial dysmorphism with dystonia. MRI of the brain was normal. Thyroid profile showed low free T4, and normal TSH but high free T3. Hence, AHDS was suspected and was confirmed by targeted next-generation testing and Sanger sequencing.

**Keywords:** Allan Herndon Dudley syndrome, central hypothyroidism, dystonia, SLC16A2

**Introduction**

AHDS is a rare X-linked recessive mental retardation syndrome that was first described in 1944. It is caused by a mutation in SLC16A2 and is also known as monocarboxylate transporter 8 gene (MCT8).[1] Mutation in this gene results in AHDS, which is characterized by delayed neurocognitive development with the abnormal thyroid function test (TFT).[1] It is a very rare disease with a prevalence of less than 1 per 10,00,000. It is commonly misdiagnosed as cerebral palsy and central hypothyroidism; hence, we are reporting this child.

**Case**

A 21-month-old male child, born of a nonconsanguineous married couple, presented with developmental delay and intermittent stiffness of limbs. He was delivered at full term with a birth weight of 3.2 kg without any complications. This child had not achieved neck holding, had intermittent opening of palms but had not acquired palmar grasp. He had stranger anxiety and responded to his name. He only cooed but did not utter a syllable. Hearing and vision were normal. There was no history of encephalopathy, seizures, diurnal variation of symptoms, and autonomic instability. There was no family history of similar complaints.

On examination, weight, length, and head circumference were 11.2 kg (-0.12SD), 92 cm (+2.76SD), and 44.3 cm (-2.54SD), respectively. He had bifrontal narrowing, abnormally shaped ear pinna, depression over helix [Figure 1A], high arched palate, non-paralytic convergent squint in left eye, and pes planus. He had spasticity and dystonia in all limbs [Figure 1B]. Power was 3/5 (MRC grade) in all groups of muscles, and he had brisk deep tendon reflexes.

Since there was no history of birth asphyxia and neonatal hyperbilirubinemia, a possibility of neurometabolic disorder was maintained. Metabolic workup (arterial blood gas analysis, lactate, ammonia, and tandem mass spectrometry) was normal. MRI of the brain showed hyperintensity on T1WI [Figure 2A] and an

**Address for correspondence:** Dr. Vyakuntaraju Kammasandra Gowda, Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Bengalure, Karnataka 560029, India. E-mail: drknvraju08@gmail.com

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alternating pattern of hyperintensity and hypointensity on T2WI [Figure 2B], which was suggestive of delayed myelination. The myelination of the genu of the corpus callosum is also incomplete. Thyroid function tests showed low free T4, 0.57 ng/dl (0.89–1.76 ng/dl); low total T4, 3.30 mcg/dl (7.3–15 mcg/dl); and normal TSH, 3.33 mIU/ml (0.34–5.6 mIU/ml) suggestive of central hypothyroidism. As child does not have any features suggestive of hypothyroidism and also had dystonia, hence considered possibilities of AHDS. Analysis of further thyroid function tests showed high free T3, 7.17 pg/ml (2.3–4.2 pg/ml) and high total T3, 2.86 ng/ml (1.05–2.69 ng/ml). Targeted next-generation sequencing showed a missense hemizygous pathogenic variant in the SLC16A2 gene, causing the substitution of arginine for glycine (c.1468G>C/p.Gly490Arg) and confirmed by Sanger sequencing.

**DISCUSSION**

TH is critical for normal brain development. Since the action and metabolism of TH occurs intracellularly, transporter proteins are required for transportation of this hormone across the cells. Defects either in the transport of TH across the cell membrane or in the metabolism or action of TH through the nuclear receptor cause impaired sensitivity of TH. The MCT8 or SLC16A2 encodes a thyroid hormone transporter that facilitates the movement of TH across the neurons.[1] Mutation in this gene leads to a lack of T3 and T4 entry in the brain, which causes central thyroid hormone deficiency. In other tissues such as muscles, heart, skin, and bowel, clinical signs suggest decreased thyroid hormone availability with peripheral dysthyroidism.[2,3] Usually, affected boys present with signs and symptoms of thyroid hormone deficiency as well as its excess and this is because of cell-specific differences in the expression of transporters.[3] The child discussed in this article had features of central thyroid deficiency, including global developmental delay and abnormal tone but no signs of peripheral dysthyroidism such as excessive sweating, weight loss, cold intolerance, dry skin, constipation etc.[4] Such children may have dysmorphism, such as bifrontal narrowing, narrow face, cupped ear pinna, high arched palate, myopathic facies, pes planus, and valgus.[1-6] They have mild to severe cognitive impairment, with infantile hypotonia evolving to spasticity or dystonia within a few years of life.[1-6] Other features include low muscle mass, rigidity, choreoathetosis, paroxysmal dyskinesia, hyperreflexia, nystagmus, ataxia, seizure, and feeding difficulties. This child had facial dysmorphism with pes planus, spasticity and dystonia, and hyperreflexia. MRI brain is usually normal or shows delayed myelination, cerebral atrophy, and thinning of corpus callosum.[4] In this child, MRI brain was normal. We diagnosed based on clinical features of global developmental delay, abnormal tone, normal birth history, normal MRI of brain with abnormal thyroid functions suggestive of AHDS and confirmed by genetic testing. Since it is a transporter defect, peripheral dysthyroidism cannot be managed with thyroxine replacement and antithyroid medications. Diiodothyropropionic acid, a cerebral agonist of T3, has been tried in some patients, showing efficacy on cardiac frequency but no neurological improvement.[7] Therapy with Triiodothyroacetic acid is now under trial. Diagnosis is especially important, as cerebral palsy and thyroid disorders are commonly misdiagnosed as the two most common pediatric disorders.

To conclude, AHDS should be considered in any male child presenting with global developmental delay and tone abnormalities such as cerebral palsy without perinatal complications, normal neuroimaging, and thyroid functions suggestive of central hypothyroidism with increased FT3.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/ have given his/ her/ their consent for his/ her/ their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due anonymity will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

Author Contribution
VK was involved in supervision, guidance and reviewed the article.
PG was involved in the management of the child and the preparation of the article.
SS provided valuable inputs in the management of this child.
NB was involved in the diagnosis and management of the child.

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