“Allan–Herndon–Dudley syndrome in a patient with Global delay development –a case report”

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Abstract

Allan-Herndon-Dudley syndrome (AHDS) is a rare X-linked recessive intellectual disability syndrome with neuromuscular involvements. Altered thyroid function tests are major milestones in AHDS diagnosis. However, in this study, we report a three-and-a-half-year-old boy with AHDS diagnosis and a novel mutation (c. 1026G>A) in SLC16A2 gene manifesting normal levels of T3, T4, and TSH. The mutation causes no change in amino acid sequence, but affects splicing through alteration of an exonic splicing enhancer. To the best of our knowledge, there are only two similar reports in the literature. It is concluded that altered levels of thyroid hormones are notable but not necessary markers for diagnosis of AHDS. The candidate diagnosis of AHDS should be considered in patients with X-linked recessive intellectual disability syndrome with neuromuscular involvements irrespective of levels of thyroid hormones; otherwise, it could lead to under-diagnosis of the disorder.

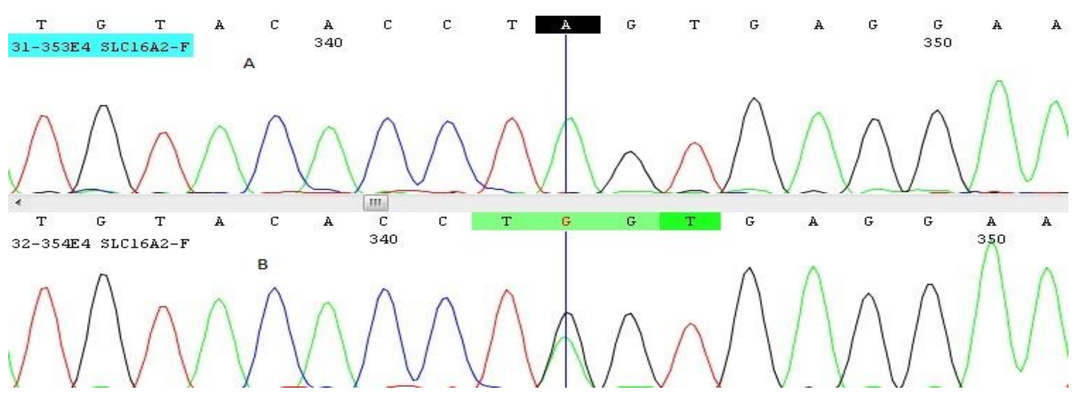
Introduction

Allan-Herndon-Dudley syndrome (AHDS) is an X-linked recessive intellectual disability syndrome characterized by muscular hypoplasia, hypotonia, spastic paraplegia (1). AHDS is a rare disease with overall prevalence less than one in a million. The disease manifestations appear in the neonatal period or early infancy. AHDS is caused by mutations in the SLC16A2 gene (Xq13.2). This gene encodes for monocarboxylate transporter 8 (MCT8) which is a specific transporter of thyroid hormone T3 into nerve cells (2). Diagnosis is based on clinical manifestations, delayed myelination of the brain on MRI radiological examination, and the presence of altered thyroid function tests. Affected males have abnormally high T3 levels, low to normal T4 levels, and normal to slightly elevated TSH levels. Diagnosis is confirmed by molecular genetic testing revealing mutations in the SLC16A2 gene. In this study, we report a three-and-a-half-year-old boy with AHDS diagnosis and a novel mutation in SLC16A2 gene manifesting normal levels of T3, T4, and TSH.

Case presentation

A three-and-a-half-year-old boy referred to our clinic, for evaluation of floppiness. He was also under observation of pediatric neurologist because of cerebral palsy. He was born from unrelated parents; delivery occurred in 38 weeks, with a birth weight of 2.9 kg and length of 50cm. His progressive weakness was discovered a few months after birth. On our examination, he manifested a failure to thrive: his weight was 11 kg (< 5th percentile of corresponding age) and his length was 87cm (< the 5th percentile of corresponding age). The head circumference was 47.5 cm (equal to the 50th percentile), though. He manifested excessive drooling, obvious head lag and global developmental delay implying a serious neurological damage. He could follow objects and pay attention to sounds, but he was unable to walk, speak and feed independently. Other neuromuscular findings involved generalized hypotonia, hypotonia of limbs and increased deep tendon reflexes. Genitalia was prepubertal and testes were descended and palpable. Laboratory tests revealed normal metabolic and lipid profile, normal liver function tests, and normal levels of serum triiodothyronine (T3), thyroxine (T4) and TSH. ABR (Auditory brainstem response) test showed no abnormal latency time, but brain MRI showed remarkable delayed myelination of the brain white matter. The mother disclosed that from another marriage she had another son with similar phenotypes who had died at the age of five. This familial occurrence suggested an X-linked recessive disorder, but because AHDS was not suspected before analysis, exome sequencing was performed. After receiving written informed consent from the patient’s family, patient’s blood sample was obtained and genomic DNA was extracted. Clinical exome sequencing was performed using Illumina HiSeq4000 sequencing panel. Finally, a single nucleotide alteration in exon 3 (c.1026G>A), was considered as the mutation related to the patient’s condition. The mutation does not cause any change in amino acid sequence (p. L342L). Using Mutation Taster, the variant was predicted as damaging. Using HSF (Human Splicing Finder), the mutation was predicted to alter a wild type splicing donor site, most probably affecting splicing through alteration of an exonic splicing enhancer (ESE). This mutation was confirmed by Sanger sequencing.

The same mutation was confirmed in the patient’s mother. Therefore, the diagnosis of AHDS was confirmed in the family.



Discussion

The AHDS is a rare X-linked recessive intellectual disability syndrome. The AHDS accounts for 1-2 percent of males with intellectual disability. The diagnosis is primarily based on clinical findings and altered thyroid hormone levels. Although the increased T3 levels are already mentioned as an obligate finding in some studies (3, 4), to the best of our knowledge, there are two previous studies supporting normal levels of thyroid hormones in AHDS patients (5, 6). In this study, we report a three-and-a-half-year-old boy with a novel mutation in SLC16A2 gene manifesting AHDS and normal thyroid function tests.

The fact that why some patients with AHDS manifest normal thyroid hormones is unclear. A previous study shows that a single mutation in SLC16A2 gene in two males in a family caused phenotypic variability: the infant male showed increased T3 levels and the adult male showed normal T3 levels (5). The authors infer that this could probably be attributed to the age of the patients. However, in our study, we report a three-and-a-half-year-old infant with normal levels of all thyroid hormones.

The normal thyroid hormones profile in some AHDS patients implies clinicians should consider AHDS as a candidate diagnosis in patients with X-linked recessive intellectual disability syndrome with neuromuscular involvements irrespective of levels of thyroid hormones. Screening for mutations in SLC16A2 gene in these cases obviates the need for expensive whole exome sequencing (WES). This is particularly important in developing countries where WES is still costly due to limited resources. Furthermore, this screening is essential from the view of genetic counseling. Since there is no treatment available for this disease and the disease compromises the quality of life by affecting the ability of the patient to live independently, genetic counseling to prevent the birth of an affected child really matters. Affected families should be informed that prenatal or preimplantation diagnosis of a male with AHDS is possible if the mutation in his mother is identified. In our case, ultimate diagnosis of AHDS in one infant uncovered his previously undiagnosed affected brother who had died of the disease. If the candidate diagnosis of AHDS was considered in the first brother, it could have led to prenatal or preimplantation diagnosis to prevent the birth of a second affected child.
In brief, due to phenotypic variations in the levels of thyroid hormones in AHDS patients, we believe that the disorder is often under-diagnosed imposing economic and mental burden.

Learning points:

Altered levels of thyroid hormones are notable but not necessary marker for diagnosis of AHDS. AHDS is often under-diagnosed and this is due to variable phenotypes such as the variable levels of thyroid hormones. The candidate diagnosis of AHDS should be considered in patients with X-linked recessive intellectual disability syndrome with neuromuscular involvements irrespective of levels of thyroid hormones

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