ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2022;93(3):428-433
DOI: 10.32641/andespediatr.v93i3.3904

CLINICAL CASE

Allan-Herndon-Dudley syndrome: a diagnosis to rule out in any male infant with undiagnosed hypotonia

Síndrome de Allan-Herndon-Dudley: un diagnóstico a descartar ante todo lactante varón con hipotonía sin causa determinada

David Molina Herranz[a,b], Amelia Moreno Sánchez[a,b], María Violeta Fariña Jara[a,b], Raquel Pérez Delgado[a], José Ignacio Labarta Aizpún[b], Silvia Sánchez Marco[c], Silvia Izquierdo Álvarez[d], Javier López Pisón[a]

[a]Servicio de Pediatría, Sección de Neuropediatría y Metabolismo, Hospital Universitario Miguel Servet. Zaragoza, España.
[b]Servicio de Pediatría, Sección de Endocrinología Pediátrica, Hospital Universitario Miguel Servet. Zaragoza, España.
[c]Servicio de Pediatría, Sección de Neuropediatría, Hospital Obispo Polanco. Teruel, España.
[d]Servicio de Bioquímica Clínica, Sección de Genética Clínica, Hospital Universitario Miguel Servet. Zaragoza, España.

Received: July 1, 2021; Approved: December 23, 2021

What do we know about the subject matter of this study?

Allan-Herndon-Dudley syndrome is a rare X-linked genetic disorder caused by deficiency of the MCT8 transporter, specific for thyroid hormones mainly at the cerebral level. It causes a severe neurological picture of early onset with muscular hypotonia.

What does this study contribute to what is already known?

We present a case of unexpected diagnosis of MCT8 transporter deficiency, which highlights the usefulness of performing a complete thyroid profile with free T3 levels in any male infant with hypotonia and muscle weakness without a specific cause.

Abstract

Allan-Herndon-Dudley syndrome is a rare X-linked genetic disorder, caused by a deficiency of the monocarboxylate transporter 8 (MCT8), a specific transporter of thyroid hormones, with functions mainly at the brain level. The syndrome produces an early onset of severe neurological disorder, in which hypotonia predominates. **Objective:** To present a rare case with an unexpected diagnosis, highlighting the usefulness of requesting a complete thyroid profile in every hypotonic male infant without a specific cause. **Clinical Case:** A 10-month-old male infant with severe axial and peripheral hypotonia, global weakness with little spontaneous mobility, without head support or stable sitting. Complete metabolic and peripheral neurophysiological studies were performed. Genetic studies for spinal muscular atrophy, Prader Willi syndrome, and myotonic dystrophy were also performed. The trio exome analysis detected a probably pathogenic variant c.359C>T;p.(Ser120Phe), hemizygous in exon 1 of the *SLC16A2* gene, inherited from the mother. Thyroid abnormalities as increased free

Keywords:
Allan-Herndon-Dudley Syndrome; Brain Hypothyroidism; Hypotonia; Monocarboxylate Transporter 8; SLC16A2; Thyroid Hormones

Correspondence:
David Molina Herranz
dmolinaherranz@gmail.com

Edited by:
Carolina Heresi Venegas

How to cite this article: Andes pediatr. 2022;93(3):428-433. DOI: 10.32641/andespediatr.v93i3.3904

triiodothyronine (T3) and thyroid-stimulating hormone (TSH), and delayed myelination were observed. **Conclusions:** MCT8 deficiency should be considered in the case of the male infant with unexplained hypotonia and weakness without a determined cause. The diagnosis is guided by a thyroid profile including free T3 hormone, because it presents a characteristic thyroid profile with decreased free thyroxine (T4), increased free T3, and normal or slightly elevated TSH levels. In this case, the implementation of the trio exome analysis allows establishing an early certain diagnosis.

Introduction

Thyroid hormones regulate very important aspects of central nervous system development and metabolism. Triiodothyronine (free T3) is the active form and comes from the peripheral conversion of thyroxine (free T4). There are different proteins with thyroid hormone transporting action, the most relevant being monocarboxylate transporter 8 (MCT8), with expression in certain tissues such as the basolateral membrane of thyroid follicles where it favors hormone secretion or in the central nervous system as the main transporter at the neuronal level; therefore, this protein is essential for normal brain development[1,2]. In addition, thyroid hormones, mainly free T3, control the expression of genes involved in myelination, differentiation, migration, and cell signaling[3].

The SLC16A2 (solute carrier family 16 member 2) gene, located on the X chromosome (Xq13.2), is the gene encoding the MCT8. Although most mutations lead to an almost complete absence of the transport function of MCT8, there is some residual activity in some of them associating a less severe phenotype, related to the degree of genetic penetrance[1,4,5]. Some mild cases have been described in women, probably related to biases in the inactivation of the X chromosome[2,6].

This protein is a highly specific transmembrane transporter for thyroid hormones and is essential for internalizing them into target organ cells[1,2]. MCT8 deficiency is known as Allan-Herndon-Dudley syndrome (AHDS) (OMIM#300523; ORPHA#59) and has an unknown prevalence[7]. It is a severe X-linked neurological disorder affecting males. It causes, on the one hand, a severe hypothyroid state in MCT8-dependent cells such as those of the brain, and on the other hand, due to elevated free T3 levels, local hyperthyroidism in less MCT8-dependent tissues such as heart, muscle, liver, or kidney (Table 1)[2,6,8,9].

The neurological picture associates significant axial hypotonia, neurodevelopmental disorder, and pyramidal and extrapyramidal involvement[1,2]. However, the pathogenesis of the neurological picture is unknown and difficult to study in mice because they compensate for cerebral hypothyroidism through another transporter[10,11].

These patients present a characteristic thyroid profile with decreased free T4 and rT3 (reverse T3), increased free T3, and normal or slightly elevated thyroid-stimulating hormone (TSH) levels[1-11,12]. Although MCT8 also transports free T4, it can pass through the blood-brain barrier by other thyroid transporters, which may explain its low blood levels. MCT8 participates in the regulation of free T4 and T3 secretion by the thyroid, and in its absence, they accumulate in this organ. On the other hand, the increase in circulating free T3 increases type 1 deiodinase activity in the liver and kidneys, which increases the conversion of T4 to free T3, generating a greater decrease in circulating free T4 and an increase in free T3[1,2,4,11]. The slight elevation of TSH in the presence of decreased levels of free T4 and elevated levels of free T3 would be related to the expression of MCT8 at the hypothalamic level since its deficiency interferes with the negative regulation of the thyroid axis at the hypothalamic-pituitary level[4].

The treatment for MCT8 deficiency with the administration of thyroid hormone analogs capable of reaching the cell nucleus via an alternative transporter to MCT8 is under investigation[9]. The objective of this report is to present a case diagnosed in our hospital, highlighting its clinical presentation and the importance of the genetic study (exome trios) to establish the diagnosis.

Clinical Case

A 10-month-old male infant was referred to our hospital due to axial and peripheral hypotonia. The patient had a history of an uneventful pregnancy, with normal prenatal ultrasound, term newborn, weighing 3,840 grams and length 51 cm. The neonatal screening was normal, with a TSH level of 3.6 μIU/mL. He was the only child of healthy, non-consanguineous parents, and his family history included two siblings of the maternal grandmother with disabilities and a maternal uncle diagnosed with hypoxic-ischemic encephalopathy.

Physical examination at 10 months showed a length of 72 cm (-0.83 SDS), weight of 7.66 kg (-1.92 SDS)[13], and head circumference of 45 cm (-0.96 SDS). He pre-

Table 1. Clinical features of MCT8 deficiency in different tissues with transporter deficiency

Location	Organ-tissue	Symptoms
CNS - Hypothyroidism clinic	Vascular endothelium BBB	Developmental delay, intellectual disability
	Neurons	
	Pituitary	Alteration of thyroid hormone axis and TSH
Peripheral organs - Hyperthyroidism clinic	Thyroid	Impaired synthesis and secretion of thyroid hormones (free T4 and free T3)
	Liver	SHBG increase, cholesterol decrease
	Kidney	Decreased creatinine
	Cardiovascular	Tachycardia, hypertension, premature atrial complexes
	Musculoskeletal	Loss of muscle mass, osteopenia, decreased creatinine levels
	General	Weight loss, increased sweating, hypermetabolism

Abbreviations: BBB: blood-brain barrier; CNS: central nervous system; free T3: triiodothyronine; free T4: thyroxine; TSH: thyroid-stimulating hormone; SHBG: sex hormone-binding globulin.

sented a morphological phenotype with long eyelashes, slightly tent-shaped mouth, and slight hypertelorism. Social contact was adequate. He had severe axial hypotonia and moderate peripheral hypotonia, with global weakness. He had incomplete and intermittent head control, no stable sitting or turning, being only capable of small autonomous crawling movements. Sitting with assistance showed a marked kyphosis (Figure 1). Spontaneous mobility was poor, especially at the proximal extremities, with difficulty in lifting limbs, indicative of significant generalized weakness. In the supine position, he adopted an "open-book" posture, with abducted hips. In the pull-to-sit maneuver, head lag was observed. Tendinous reflexes were present and symmetrical.

A study was initiated with the following complementary examinations all of which presented normal results: metabolic profile including TSH, free T4, vitamin B12, copper, ceruloplasmin, homocysteine, serum amino acids, CDT test (carbohydrate-deficient transferrin), ammonium, lactate, organic acids, and SAICAr test (succinylaminoimidazole carboxamide riboside) in urine and very-long-chain fatty acids. Also, biotinidase activity and Pompe's enzyme study were performed as well as abdominal ultrasound, cardiological study, eye fundus examination, electroencephalogram, electroneurogram, and electromyography, auditory evoked potentials, protocolized genetic study for hypotonic picture of Spinal Muscular Atrophy, Prader Willi and Myotonic Dystrophy type I, and array comparative genomic hybridization (aCGH), all without abnormalities. Empirical treatment with riboflavin was started.

At 13 months of age, a brain MRI (figure 2) was performed which showed delayed anterior white matter myelination, mainly subcortical and U-shaped fibers, visualized as hyposignal in T1 and MP2RAGE sequences and subtle hypersignal in T2 sequence.

Given the absence of an etiological diagnosis in an infant with significant postural and muscle tone involvement, it was decided to perform a trio exome analysis, which detected a hemizygous missense variant in exon 1 of the gene *SLC16A2* c.359C>T; p.Ser120Phe, which is associated with AHDS with X-linked inheritance pattern. The mother presented a heterozygous variant.

Once the etiology was established, the thyroid study was repeated and completed as follows: TSH 9.31 µIU/mL (Normal value (NV): 0.38-5.33), free T3 6.58 pg/mL (NV 2.57-4.92), free T4 0.83 ng/dL (NV: 0.58-1.64), antithyroid antibodies (antithyroglobulin, antithyroperoxidase, and TSH receptor), and thyroglobulin all within normal range, and thyroid ultrasound without findings. The patient also had increased SHBG levels with 350.20 nmol/L (NV: 13.50-71.40). Electrocardiogram, echocardiography, and nutritional screening were performed before initiating the treatment with thyroid hormone analog.

According to the recommendation of experts and following a national protocol, treatment was started with 3,3',5-triiodothyroacetic acid (Triac). At the time of initiation, when the patient was 19 months old, he presented anthropometry with a length of 84.5 cm (0.24 SDS) and weight of 9.42 kg (-2.03 SDS)[13]. The objective to be achieved with this treatment was to reduce as much as possible both the symptomatology of peripheral hyperthyroidism and the impact of the deficit on the development of the central nervous system. The initiation of Triac treatment in this patient is recent, and it is not yet possible to evaluate the response to it.

Discussion

There are currently about 320 diagnosed cases of AHDS described in the literature[6]. Although the preva-

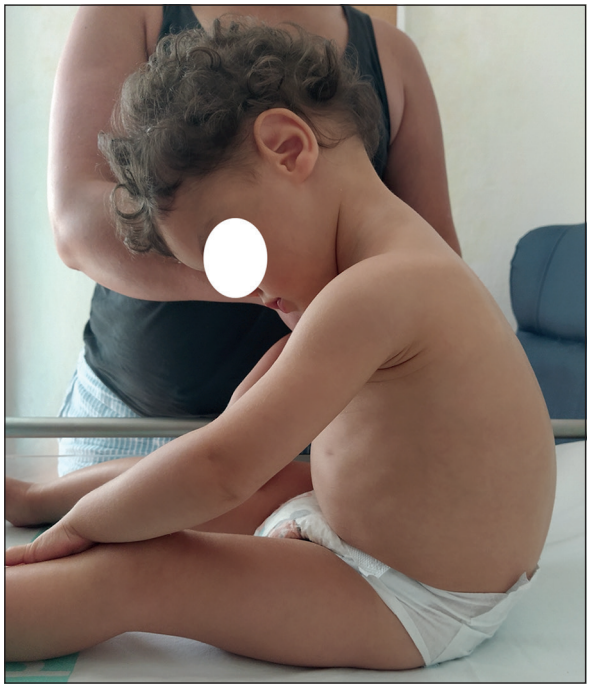

Figure 1. Dependent sitting. Needs support by a caregiver to maintain sitting. Axial hypotonia and muscle weakness result in marked kyphosis and forward head droop at rest.

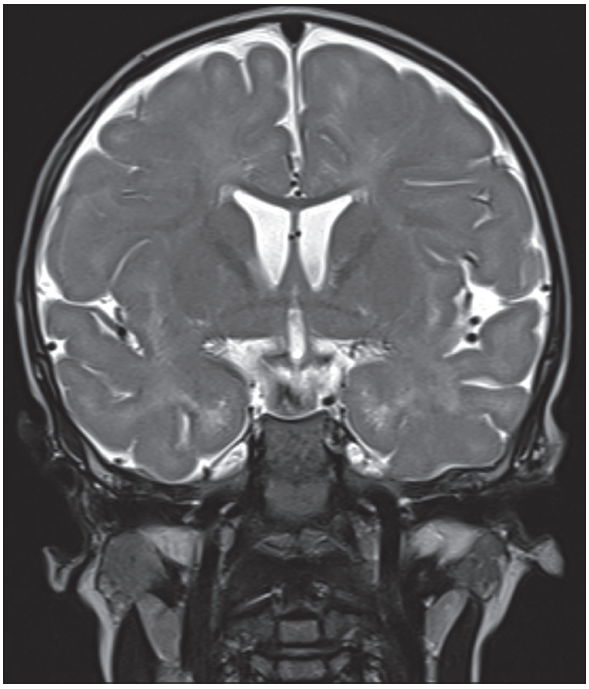

Figure 2. Brain MRI, coronal section, T2 sequence. Hyperintensity of the fundamentally subcortical white matter and U-shaped fibres, compatible with hypomyelination. The corpus callosum is correctly myelinated.

lence is unknown[7], the estimate is 1/70000 males and 1.4% with intellectual disability of unknown etiology[12]. Up to 4% of X-linked intellectual disability syndromes could be associated with *SLC16A2* gene mutations[2,6].

The confirmatory diagnosis of this entity is genetic, demonstrating the presence of an alteration in the *SLC16A2* gene. However, in the case of a male with compatible clinical manifestations, the diagnosis can be guided by a thyroid profile[2,7,9,12]. In our case, initially, no thyroid profile alteration was detected because the metabolic profile requested in the case of suspected neuromuscular disease did not include the determination of free T3 levels. Subsequently, after the genetic finding, the thyroid profile was repeated including free T3 levels that were altered. It is likely that if this determination had been added initially, the diagnostic process would have been earlier. Therefore, the determination of free T3 levels has now been included in our hospital in the study of the child with possible neuromuscular pathology, along with all the tests performed in our case.

Most of these children affected by AHDS are born at term, with weight, length, and head circumference within normal ranges and, due to mechanisms not well known, do not show signs of congenital hypothyroidism[2]. Normal or slight elevation of initial TSH levels means that TSH-based neonatal screening does not allow early detection, so clinical suspicion is important[1]. In these patients, hypotonia begins to manifest in the first 6 months of life, many do not even reach head control, some are unable to move their limbs, and most of the children cannot sit upright. Some patients can walk, exceptionally before the age of 3 years, but with an ataxic gait that requires support[1,2,5,9]. Hypotonia, which is present in 100% of cases[11], is mainly axial and progresses to spastic tetraparesis. Many patients show extrapyramidal symptoms. Less affected patients, who maintain voluntary motor function, have cerebellar symptoms such as ataxia, intention tremor, and dysmetria[1,9,12]. In addition, seizures[1,7], swallowing and feeding problems, and dysarthria may occur or often fail to develop language[1,2,5].

As described in the literature, in our patient there were no anthropometric alterations at birth or findings of hypothyroidism in neonatal screening. The progressive neurological symptoms are typical of the described picture, a consequence of the alteration of brain development due to a deficit of thyroid hormones at this level.

Although MCT8 deficiency results in a state of cerebral hypothyroidism with abnormalities in neuronal differentiation, myelination, and synaptogenesis, other tissues are in such a state, as shown in the clinical presentation in some patients (table 1)[1,2,6,8].

Due to the alterations in oropharyngeal mechanics and/or because of the hypermetabolic state resulting from peripheral hyperthyroidism, as time progresses, there is weight and height retardation and decreased muscle mass[1,2,5,9]. In this context, an increase in SHBG hormone was observed as a consequence of hyperthyroidism at the hepatic level. In terms of phenotype, elongated face, large and cupped ears, thoracic malformations, and myopathic facies have been documented more frequently. Some patients develop microcephaly over time[12].

As thyroid hormones intervene in myelination, AHDS presents an alteration of this process, although some authors claim a delay in myelination and others a hypomyelination[1,2,6]. For this reason, this condition has been classically related to Pelizaeus-Merzbacher disease, which is an X-linked leukodystrophy that causes psychomotor retardation, hypotonia, spasticity, and nystagmus[1,9].

The management of these patients should be carried out by a multidisciplinary team that provides care and follow-up of all possible alterations such as weight loss, feeding difficulties, hypotonia, psychomotor retardation, spasticity, extrapyramidal movement disorders, epilepsy, etc.[7], in addition to the monitoring of hormone levels.

Prognosis is mainly determined by recurrent infections, dysphagia, and orthopedic manifestations (kyphoscoliosis, hip dislocation, bone demineralization)[5,12]. Aspiration pneumonia and sudden death are the most frequent causes of death, although some exceed 70 years of age[5,9].

Different treatment options are being investigated, although the only ones with clinical application currently are thyroid hormone analogs (Triac). This therapy, analogous to free T3 hormone, involves molecules that enter MCT8-dependent cells via an alternative transporter. Once inside the cell, these analogs bind to the hormone's nuclear receptor in order to perform their physiological function[2,5,6,9]. In humans, analogs improve the general symptomatology of hyperthyroidism. However, only a slight improvement has been reported in children under 3 years of age in terms of intellectual disability and motor impairment[2,5,9]. Thyroid hormones tend to return to normal values by the first 12 months[9].

Allan-Herndon-Dudley syndrome or MCT8 transporter deficiency should be considered in the study of the male infant with hypotonia and weakness without a specific cause. The diagnosis is guided by a thyroid profile including free T3 hormone levels since they present a characteristic thyroid profile with decreased T4, increased free T3, and normal or slightly elevated TSH levels. The implementation of the trio exome analysis, in this case, allows an early accurate diagnosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. López-Marín L, Martín-Belinchón M, Gutiérrez-Solana LG, Morte-Molina B, Duat-Rodríguez A, Bernal J. Deficiencia del transportador celular de hormona tiroidea MCT8: caso clínico y revisión de la bibliografía. Rev Neurol 2013; 56:615-22.
2. Groeneweg S, van Geest FS, Peeters RP, Heuer H, Visser WE. Thyroid Hormone Transporters. Endocr Rev. 2020; 41: 146-201. doi: 10.1210/endrev/bnz008.
3. Bernal J. Thyroid hormones and brain development. Vitam Horm. 2005; 71:95-122. doi: 10.1016/S0083-6729(05)71004-9.
4. Groeneweg S, Visser WE, Visser TJ. Disorders of thyroid hormone transport into the tissues. Best Pract Res Clin Endocrinol Metab 2017; 31:241-253. doi: 10.1016/j.beem.2017.05.001.
5. Grijota-Martínez C, Bárez-López S, Gómez-Andrés D, Guadaño-Ferraz A. MCT8 Deficiency: The Road to Therapies for a Rare Disease. Front Neurosci. 2020; 14:380. doi: 10.3389/fnins.2020.00380.
6. Vancamp P, Demeneix BA, Remaud S. Monocarboxylate Transporter 8 Deficiency: Delayed or Permanent Hypomyelination? Front Endocrinol (Lausanne). 2020; 11:283. doi: 10.3389/fendo.2020.00283.
7. Sarret C, Oliver Petit I, Tonduti D. Allan-Herndon-Dudley Syndrome. 2010 [updated 2020 Jan]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021.
8. Krude H, Biebermann H, Schuelke M, Müller TD, Tschöp M. Allan-Herndon-Dudley-Syndrome: Considerations about the Brain Phenotype with Implications for Treatment Strategies. Exp Clin Endocrinol Diabetes. 2020; 128:414-422. doi: 10.1055/a-1108-1456.
9. Groeneweg S, Peeters RP, Moran C, et al. Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019; 7(9):695-706. doi: 10.1016/S2213-8587(19)30155-X.
10. Morte B, Ceballos A, Diez D, et al. Thyroid hormone-regulated mouse cerebral cortex genes are differentially dependent on the source of the hormone: a study in monocarboxylate transporter-8- and deiodinase-2-deficient mice. Endocrinology. 2010; 151(5):2381-7. doi: 10.1210/en.2009-0944.
11. Bernal J. Síndromes de resistencia a las hormonas tiroideas. Endocrinol Nutr. 2011; 58(4):185-96. doi: 10.1016/j.endonu.2011.02.001.
12. Remerand G, Boespflug-Tanguy O, Tonduti D, Touraine R, Rodriguez D, Curie A, Perreton N, Des Portes V, Sarret C; RMLX/AHDS Study Group. Expanding the phenotypic spectrum of Allan-Herndon-Dudley syndrome in patients with SLC16A2 mutations. Dev Med Child Neurol. 2019; 61(12):1439-1447. doi: 10.1111/dmcn.14332.
13. Carrascosa A, Fernández JM, Fernández C, et al. Estudio transversal español de crecimiento 2008: Parte II. Valores de talla, peso, índice de masa corporal en 32.064 sujetos (16.607 varones, 15.457 mujeres) desde el nacimiento hasta alcanzar la talla adulta. An Pediatr (Barc). 2008; 68:552-69. doi: 10.1157/13123287.