

**Case report**

## Severe neurological abnormalities in a young boy with impaired thyroid hormone sensitivity due to a novel mutation in the MCT8 gene

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### ABSTRACT

Monocarboxylate transporter 8 (MCT8) is an active and specific thyroid hormone transporter into neurons. *MCT8* mutations cause an X-linked condition known as Allan-Herndon-Dudley syndrome and are characterized by impaired psychomotor development and typical abnormal thyroid function. We describe a 10-year-old boy with severe cognitive disability, axial hypotonia, spastic quadriplegia and sporadic dyskinetic episodes. He initially presented with thyroid dysfunction (high FT3, low rT3, low FT4 and normal TSH) and generalized retardation of the cerebral and cerebellar myelination in brain magnetic resonance imaging. The clinical and laboratory findings led to sequencing of the *SLC16A2/MCT8* gene, which identified a novel missense mutation in exon 5. The study of peripheral markers of thyroid function suggests a paradoxical state of thyrotoxicosis in some peripheral tissues. Our patient had a typical clinical presentation at birth but because of the rarity of his disease his diagnosis was not made until the age of 7. The delay can also be explained by the omission of the free T3 assay in the first thyroid evaluation performed. This case therefore highlights the possible benefit of including the T3 assay in the study of patients with severe psychomotor disability of unknown etiology, thus eliminating extra costs for unnecessary complementary diagnostic tests.

**Key words:** Allan-Herndon-Dudley syndrome, Impaired thyroid hormone sensitivity, Low T3, MCT8, Psychomotor retardation, Severe neurological phenotype, Thyroid dysfunction, Thyroid hormone transporter

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### INTRODUCTION

Thyroid hormones (TH) are crucial for the growth and development of many organs, especially the central

nervous system (CNS), and for the regulation of the basal metabolic rate.<sup>1,2</sup> The thyroid gland produces thyroxine (T4) and a minor amount of triiodothyronine (T3). TH action is mediated by the binding of T3 to its nuclear receptor, after converting inactive pro-hormone T4 into T3 through outer ring deiodination by deiodinases 1 and 2 (D1 and D2). Deiodinase 3 (D3) inactivates T4 and T3 to reverse T3 (rT3) and 3,3'-diiodothyronine (T2), respectively.<sup>2</sup> Thus, the biological activity of T3 is determined by the activity of the deiodinases catalyzing the production or degradation of TH and by the activity of tissue specific transporters.<sup>2,3</sup>

Over the last two decades a number of TH transporters have been identified. Most of them are non-specific and interact with a wide diversity of ligands.<sup>2</sup> In 2003, Friesema *et al* described monocarboxylate transporter 8 (MCT8) as a very active and specific TH transporter.<sup>4</sup> MCT8 belongs to the monocarboxylate transporter (MCT) family and contains 12 transmembrane domains, while both N and C termini are located intracellularly.<sup>2</sup> MCT8 is expressed in the brain, heart, liver, adrenal glands, kidney and thyroid.<sup>5</sup> Analyses of MCT8 mRNA in mouse CNS by *in situ* hybridization revealed pronounced levels of neuronal populations in the cerebral and cerebellar cortex, hippocampus, striatum, hypothalamus and choroid plexus structures.<sup>6</sup> These results indicate that MCT8 plays an important role in proper brain development by transporting TH into neurons.<sup>6</sup>

The MCT8 gene is located on the X-chromosome (Xq13.2) and consists of 6 exons.<sup>7</sup> This gene contains 2 translational start sites and codes for a long or short protein of 613 and 539 amino acids, respectively, depending on which of the 2 start sites is used.<sup>2</sup> MCT8 mutations cause an X-linked condition known as Allan-Herndon-Dudley syndrome (AHDS; OMIM #300523) which is characterized by neurological impairment and abnormal thyroid function.

Here we report a young Spanish boy with AHDS due to a novel MCT8 mutation, who has a severe neurological phenotype and indirect markers of thyroid function suggesting peripheral hyperthyroidism.

## CASE REPORT

We report a 10-year-old male patient, the only

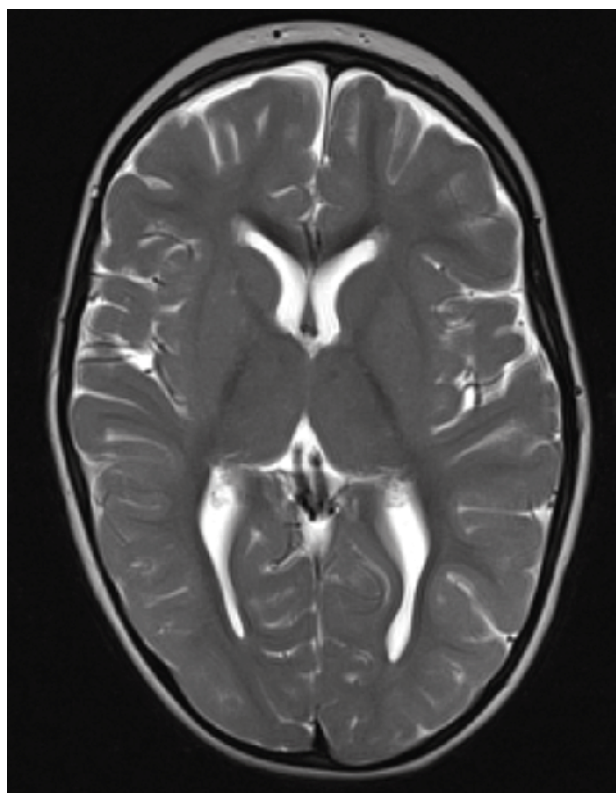
child of non-consanguineous healthy parents. There were no complications during pregnancy and an uneventful delivery occurred at 42 gestational weeks [birth weight: 3.750 g (+0.30SDS), length: 51 cm (-0.25SDS), head circumference: 34.3 cm (-1.28SDS)]. The Apgar score was 9 in the first and fifth minutes. Neonatal screening tests were normal. There was no familial history of neurological or thyroid disease. At 11 months he was admitted to the Neuropediatric ward of another hospital due to generalized hypotonia and delayed psychomotor development. The patient underwent the following tests: auditory and visually evoked potentials, karyotype, electromyography, urinary and plasma amino acids and urinary organic acids assay. All results were normal. Brain magnetic resonance imaging (MRI) revealed diffuse cortical and subcortical atrophy with passive ventricular dilatation and normal myelination for his age. The generalized hypotonia was followed by hypertonia of the limbs, articular spasticity and dystonic movements of the oromandibular region, neck and limbs.

When the child was 3 years old, his parents noticed multiple daily episodes of paroxysmal dyskinesia for a few seconds that occurred during both wakefulness and sleep, without apparent triggers. The MRI repeated at this age showed marked delay in myelination, with normal myelination of the corpus callosum and internal capsule limbs. Thyroid function evaluation performed at 6 years old showed normal results (TSH 2.41 mUI/L; T4L 0.89 ng/dL).

The patient started to be followed in the Pediatric Neurology Division of our Center when he was 6 years and 4 months old, presenting at that stage with severe intellectual and motor disabilities, being unable to speak or walk. Dysmorphic features including elongated myopathic facies, retrognathia, esotropia and large ears were noted. On neurological examination he presented with hyperextension and lateral rotation of the neck, axial hypotonia, hypertonia of the limbs with dystonic posture, choreic movements, plantar reflex in extension, patellar hyperreflexia and absent Achilles tendon reflex. He had already been medicated with levetiracetam 20 mg/kg/day and had followed an intensive program of physiotherapy since he was 1 year old. A laboratory and an MRI were requested. The electroencephalography (EEG) showed a disorganized baseline with bilateral paroxysmal slow

spike and wave activity, frequently present in both alert and asleep states. Brain MRI without contrast showed generalized retardation of the cerebral and cerebellar myelination, poor differentiation of grey and white matter also involving the basal ganglia. It also revealed a mild to moderate prominence of the supra- and infratentorial sulcus and mild ventricular dilatation, which suggested loss of brain volume (Figure 1). The fundoscopic exam was normal and no metabolic disorders were found. The laboratory examinations showed normal hematological and blood chemical values. Thyroid function tests revealed normal levels of serum TSH (1.46 mUI/L, normal range 0.35-5.5), low FT4 (0.73 ng/dL, normal range 0.89-1.8) and high FT3 (8.02 pg/dL, normal range 2.3-4.2).

The clinical findings as well as the thyroid function abnormalities suggested an impaired sensitivity to thyroid hormone, namely AHDS. This possibility led to the sequencing of the *SLC16A2/MCT8* gene



**Figure 1.** Brain MRI. Generalized retardation of the cerebral and cerebellar myelination, poor differentiation of the grey and white matter in a diffuse way and of the basal ganglia.

through Next-Generation Sequencing, which identified a novel hemizygous mutation at nucleotide position 1384 in the coding sequence of exon 5 (c.1384G>A). This results in an amino acid substitution, i.e. in place of glycine to an arginine, in codon 462 (p.Gly463Arg). The boy's mother is a carrier of the same mutation.

At the age of 7 years the child was seen by the Pediatric Endocrinology Division where the diagnosis was confirmed (Table 1). Indirect peripheral markers of thyroid function were requested (Table 1). Physical examination showed low weight (16.5Kg; -2,03SDS), normal body length (118.5cm; -1,42SDS), no goiter, normal arterial blood pressure and tachycardia (120 bpm). Bone age was concordant (Greulich and Pyle's method). Persistent tachycardia led to cardiologic evaluation. The echocardiogram was normal and the electrocardiogram showed sinus tachycardia.

Furthermore, he has scoliosis and, due to bilateral subluxation of the coxofemoral joint resulting from severe adductor muscles contracture, he was treated with adductor tenotomy.

Over the last year of follow-up, his neurological clinical picture became worse, with abrupt eye opening during sleep and increased lower limb spasticity. Currently, the patient is medicated with levetiracetam 23 mg/Kg/day and trihexyphenidyl 2 mg/day without reported side effects and with a slight improvement of the paroxysmal dyskinesia.

**Table 1.** Thyroid function and indirect peripheral markers of HT action. Description: TSH - thyroid-stimulating hormone; FT4 and FT3 – free T4 and T3. SHBG - Sex hormone-binding globulin; RBP - Retinol-binding proteins

Laboratory results		Normal values range
TSH	2.19 mUI/L	0.35-5.5
FT4	0.44 ng/dL	0.89-1.8
FT3	8.99 pg/mL	2.3-4.2
T3r	0.04 ng/mL	0.09-0.35
Total cholesterol	114 mg/dL	120-255
SHBG	180 nmol/L	10-57
Prealbumin	12 mg/dL	20-40
RBP	1.4 mg/dL	3-6
Ammonemia	39 umol/L	1-40
Lactate	1.63 mmol/l	0.33-1.33

## DISCUSSION

In 1944, AHDS was described for the first time in 24 family members with marked retardation in psychomotor development and thyroid dysfunction.<sup>8</sup> About 64 years later, it was discovered that a *MCT8* gene mutation was responsible for this clinical and laboratory picture.<sup>9,10</sup> The clinical picture of these patients is characterized in the first years of life by generalized hypotonia, poor head and neck control and failure to ambulate independently.<sup>9,11</sup> Usually, generalized hypotonia is followed by axial hypotonia associated with spastic quadriplegia and muscle atrophy. The upper and lower limbs become hypertonic and spastic and may adopt fixed dystonic positions.<sup>11</sup> During childhood, there is severe cognitive disability manifested through the absence of speech development and rudimentary communicative abilities.<sup>11,12</sup> Our patient presented a severe neurological phenotype<sup>13,14</sup> matching most of the clinical features already described in the literature. At the age of 4, the patient started having dyskinetic episodes lasting a few seconds, which occurred during both awake and sleep states without apparent triggers. These attacks have already been reported in other patients,<sup>13,15-17</sup> which were described as paroxysmal kinesigenic dyskinesia episodes that may occur as a response to an emotional or physical trigger.<sup>13</sup>

The hallmark of AHDS is the typical thyroid function profile consisting of elevated FT3, normal/low or low FT4 and normal or slightly elevated TSH.<sup>9-12,16-18</sup> Our patient exhibited high FT3, low FT4 and normal TSH, which are very suggestive of AHDS. The previous tests of our patient showed normal TSH and FT4 levels. The repetition of thyroid function tests including FT3 led to its diagnosis. Speculatively speaking, the time lag detected in the FT4 value could be interpreted as the result of laboratory interference, the use of different assay methods or the normal variations of thyroid function in these patients. Thus, a full evaluation of thyroid function is critical for the diagnosis of this clinical entity.

The major neuroradiological feature in patients with AHDS appears to be the delayed myelination, which is in agreement with the case we describe.<sup>19-22</sup> This finding is not pathognomonic<sup>22</sup> and may impose difficulties in the differential diagnosis, specifically

in the differential diagnosis for hypomyelinating leukodystrophy.<sup>20</sup> Regarding hypomyelinating leukodystrophy, two MRIs performed at an interval of at least 6 months will not show changes in the hypomyelination pattern.<sup>21</sup> Unfortunately, we did not have access to the previously performed brain MRI images in order to compare the evolution of myelination in our patient. Along with these changes in myelination, the MRI performed at the ages of 1 and 7 years old showed findings which were consistent with loss of brain volume. Similar imagiologic findings of cortical atrophy have previously been described, which points to the possibility that these patients may present a concomitant neurodegenerative process due to *MCT8* deficiency.<sup>17,23,24</sup>

Since 2004, multiple mutations of the *MCT8* gene in several families have already been reported.<sup>25</sup> These include large deletions leading to the loss of one or more exons; smaller frame-shift deletions, triplet or 1 amino acid deletions or insertions; *nonsense* mutations causing a premature truncation of the protein and *missense* mutations resulting in amino acid substitutions.<sup>25</sup> Ahmet Anik et al. described two unrelated families with AHDS, whose genetic analysis identified a *missense* mutation in exon 5 (c.1484G>C, p.G495A) and a deletion comprising exons 3 and 4. The functional analysis *in vitro* was restricted to the *missense* mutation. They concluded that the c.1484G>C, p.G495A mutation produces a defect in transport activity, especially in JEG3 cells when compared with COS1 cells, suggesting an impaired TH transport depending on the cell context.<sup>17</sup> Surprisingly, they also report that both identified mutations (the *missense* mutation and the devastating *MCT8* deletion) result in an equally severe picture of psychomotor retardation.<sup>17</sup> Our patient was identified as having a novel *missense* mutation in exon 5 (c.1384G>A, p.G463A). Although it was not possible to perform the functional analysis of the mutation using an *in vitro* assay, p. G643A is highly conserved across various species. *In silico* analysis, including SIFT, Polyphen-2, LRT and MutationTaster, classifies this variant as pathogenic. This mutation has not been reported previously and it is not present in online databases.

According to the literature,<sup>6,9,11,26</sup> the AHDS diagnosis of our patient is supported by the highly sugges-

tive clinical picture, the characteristic change in the thyroid function tests, the generalized retardation of the cerebral and cerebellar myelination in MRI and the detection of a mutation in the *MCT8* gene with X-linked inheritance.

During our patient's follow-up, we perceived a disparity in the relation between height (P10-25) and weight (<P3), despite adequate caloric intake. The low weight, the muscle atrophy and the mild persistent tachycardia (heart rate ~100-120 bpm) led to the measurements of indirect markers of thyroid function at a peripheral level. The results were consistent with a state of increased catabolism in the liver (high SHBG, low cholesterol) and at the musculoskeletal level (high lactate and ammonemia).<sup>24</sup> These findings have already been described in other patients with AHDS.<sup>17,24</sup> The presence of persistent and documented tachycardia in the ECG suggests a state of thyrotoxicosis. Our case differs in this regard from other cases described, in which the patients' cardiac results were not diagnostic.<sup>16,24</sup> On the other hand, and according to what has previously been published,<sup>11,12,17</sup> the normal growth and the correlation between bone age and chronological age suggest that *MCT8* does not play a crucial role in the transport of T3 to bone cells.<sup>11,12,17</sup> Despite T3 deficiency at the neuronal level, a state of peripheral hyperthyroidism may be explained by the possible presence of TH transports in those tissues.<sup>17,27</sup>

In summary, we describe the case of a 10-year-old boy with axial hypotonia, spastic quadriplegia, sporadic dyskinetic episodes, severe cognitive disability, low weight, severe muscle hypotonia and thyroid dysfunction (high FT3, low rT3, low FT4 and normal TSH) due to a novel *missense* mutation in the *MCT8* gene. Despite the characteristic neurological clinical picture, the diagnosis was not possible until the age of 7. Apparently, this was due to a number of factors: 1) the differential diagnosis of the X-linked cognitive disability which is vast and complex, 2) the absence of pathognomonic imagiologic features and 3) the omission of the FT3 assay in the first thyroid evaluation performed.

Current neonatal screening fails to detect these patients since it is based only on the TSH assay. This case thus contains a recommendation regarding

the possible benefit of including the T3 assay in the study of patients with severe intellectual and motor disability of unknown etiology. Besides allowing an early diagnosis and appropriate genetic counseling, this measure could reduce the extra costs involved in unnecessary complementary diagnostic tests.<sup>28,29</sup>

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