Case report

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Treatment with TRIAC in pediatric patients with MCT8

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ABSTRACT

Monocarboxylate transporters (MCTs) allow the cellular entry of thyroid hormones, especially into the central nervous system (CNS), where they are crucial for neurodevelopment. MCT8 deficiency results in the combination of hypothyroidism in the CNS and peripheral hyperthyroidism, characterized by elevated T3 levels.

The only treatment currently available is 3,3',5-triiodothyroacetic acid (TRIAC), a thyroid hormone analogue aimed at improving peripheral thyrotoxicosis and preventing the progression of neurological impairment.

Here we assess the clinical, imaging, biochemical, and genetic characteristics of 4 patients with MCT8 deficiency who have received TRIAC to date, the doses used, and the response to treatment.

Keywords: *hypothyroidism; central nervous system; thyrotoxicosis; monocarboxylic acid transporters; 3,3',5-triiodothyroacetic acid.*

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INTRODUCTION

Monocarboxylate transporters (MCTs) are transmembrane proteins that allow the flow of thyroid hormones across cell membranes, especially in the central nervous system (CNS), where they are crucial for neurodevelopment.

MCT8 is the most specific MCT for thyroxine (T4) and triiodothyronine (T3).[1] It is encoded by the *SLC16A2* gene on the long arm of the X chromosome (Xq13.2) and its deficiency results in Allan-Herndon-Dudley syndrome (AHDS), X-linked mental retardation with hypotonia or T3 resistance (OMIM 300523). MCT8 deficiency causes disease in 100% of male patients (prevalence of 1:70 000),[2] while female patients may be carriers or have mild symptoms.

Its clinical presentation is characterized by a combination of hypothyroidism in the CNS and peripheral hyperthyroidism.

From a pathophysiological perspective, the decreased cellular entry of T4 and T3 results in responses in different tissues.[1–3] Symptoms of central hypothyroidism occur at the level of the CNS, such as axial hypotonia, spasticity, and severe neurodevelopmental delay. During the course of disease, an alteration in the white matter (hypomyelination) is observed in the magnetic resonance imaging (MRI).[2]

At the level of the hypothalamic-pituitary-thyroid axis, negative feedback is altered, with normal or slightly elevated thyroid stimulating hormone (TSH) and TSH-releasing hormone (TRH). Intrathyroidal T4 is low because it is rapidly converted to T3 which is elevated, this being the main biochemical marker.

At the peripheral level, T3 may enter the tissues by alternative transporters and cause peripheral hyperthyroidism, manifested by warm skin, tachycardia, arterial hypertension (HTN), and poor height and weight growth.

The synthesis of sex hormone binding globulin (SHBG) increases and cholesterol and creatinine levels decrease; muscle hypoplasia and low creatinine kinase (CPK) levels also occur.

At Hospital J. P. Garrahan, the first patient with MCT8 deficiency was assessed in 2003, and this was the third case reported in the international bibliography.[4] Since then, 6 other patients have been diagnosed at our hospital.

The only treatment available is 3,3',5-triiodothyroacetic acid (TRIAC), a thyroid hormone analogue that crosses cell membranes without requiring the MCT8 transporter, improves clinical and biochemical signs of peripheral thyrotoxicosis, and may prevent the progression of neurological impairment.[5] Previous studies used mean doses of 38 µg/kg/day (range: 15–105).[6]

In Argentina, the use of triac was approved by the National Drug, Food and Technology Administration of Argentina (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, ANMAT) in April 2015.

The objective of this study was to assess the clinical, imaging, biochemical, and genetic characteristics of patients with MCT8 deficiency treated with TRIAC, the doses used, and the response to treatment.

MATERIALS AND METHODS

Here we report a case series of patients with MCT8 deficiency assessed at Hospital J. P. Garrahan and treated with TRIAC between January 2019 and December 2022.

Clinical characteristics

At the beginning of treatment and at the last control, age, weight and height progression, heart rate, blood pressure, feeding difficulty, neurological examination focused on neurodevelopment, and muscle tone and mass were assessed.

Hormonal determinations

TSH, free T4, and total T3 were measured using the CMIA method on Abbott's Architect i4000 Immunoassay Analyzer. The reference intervals proposed by Chaler et al.[7] were applied.

Total T4 and SHBG were analyzed by chemiluminescence on the Immulite 2000 XPi system, and the reference intervals proposed by Elmlinger et al.[8,9] were applied.

Molecular study

Genomic DNA was isolated from peripheral blood leukocytes of patients and their mothers following standard procedures on the Chemagic magnetic separation module I. For point mutation detection, the coding region (exons 1–6) and flanking intronic regions of the *SLC16A2* gene were amplified by polymerase chain reaction (PCR) and analyzed by automated Sanger sequencing. The nucleotide sequences obtained were compared with the reference sequence of the *SLC16A2* gene: NG_011641.2. The American College of Medical Genetics and Genomics (ACMG) standards[10] were used to predict the pathogenicity of previously undescribed variants.

The parents of all patients signed the informed consent for the use of TRIAC.

RESULTS

During the period from January 2019 to November 2022, 4 patients from 4 different families were diagnosed with MCT8 deficiency and treated with TRIAC at Hospital J. P. Garrahan. The data are summarized in *Table 1*.

All patients were male, with a median age at diagnosis of 1.38 years (range: 0.58–7.16). The most frequent clinical manifestations were axial hypotonia, spasticity, and overall developmental delay secondary to central hypothyroidism. Signs of peripheral hyperthyroidism were observed in 50% of patients; a lack of weight progression was the most frequent clinical manifestation. None had cardiovascular signs.

In 2 patients, the MRI showed alterations in myelination.

Elevated T3 levels (3.19–4,7 ng/mL) were observed in 100% of patients. Two had normal TSH; 1, slightly elevated TSH; and 1, inhibited TSH (receiving levothyroxine). T4 and free T4 determinations were low in 3 patients and normal in 1 (receiving levothyroxine). All patients had elevated SHBG.

Molecular studies revealed pathogenic variants in all studied patients. A carrier status was noted in 3/4 (75%) of the mothers, and 2 had mosaicism.

The mean time from diagnosis to initiation of TRIAC was 2.7 months (±2.2 months). All patients received a daily intake, with a mean dose of 19 µg/kg (±6.8 SD). T3 levels decreased in all patients, and even 3/4 reached normal values, over a mean time of 2.5 months. T4 and free T4 levels remained low in all cases and TSH levels were normal while receiving treatment.

In our population, the main benefit was the improvement in spasticity, muscle tone, and developmental delay. The 2 children with malnutrition showed an improvement in weight.

No adverse reactions to TRIAC were reported during follow-up.

DISCUSSION

As described in the international bibliography,[2] 100% of the patients had signs of central hypothyroidism. In our case series, 50% of patients had signs of peripheral hyperthyroidism as manifested by a lack of weight progression. No cardiovascular signs were observed, which differs from what has been reported by Geest et al.,[6] who found that 35% of their population had tachycardia at diagnosis.

In relation to lab tests, previous studies[2] reported that 95% of patients had elevated T3; 89%, normal TSH; and 90%, low T4 and free T4. Most of our findings are consistent with those published in international reports. The exception was P3, who had normal T4 and free T4 while receiving levothyroxine, and the elevated T3 level was evidenced during such treatment.

As for the genetic study, more than 150 variants have been described to date, including missense, nonsense, splicing, deletions, insertions, and large rearrangements. There is even a report of a woman affected by inactivation of an X chromosome.[11] In our population, 2 new pathogenic variants were identified in the *SLC16A2* gene, while the others had been previously described.[12] The presence of somatic mosaicism (mothers of P3 and P4) had been previously reported.[13]

In relation to treatment, the mean time from diagnosis to triac initiation was short, and the doses were close to the lower range that has been published. Although doses were low, a decrease in T3 levels and remarkable clinical benefits were achieved in all cases.

The limitations of this study are its retrospective nature and the limited number of patients, who were from different families with unequal access to stimulation therapies, which are a fundamental aspect in the progression of neurodevelopment.[5]

COMMENTS

In patients with neurological impairment of undefined cause (developmental delay, hypotonia) and/or delayed myelination in the MRI associated with signs of thyrotoxicosis, MCT8 deficiency should be suspected. If it is clinically suspected, a complete thyroid profile should be requested because elevated T3 levels are a characteristic biochemical marker.

In case of a compatible clinical presentation, the patient should be referred to a tertiary care hospital for confirmatory molecular study, early diagnosis, timely multidisciplinary management, and family genetic counseling.

Although MCT8 deficiency is uncommon, pediatricians, neurologists, and endocrinologists should be alerted so that they have a high level of suspicion and thus achieve a timely management to prevent the morbidity and mortality associated with thyrotoxicosis in a vulnerable population.

Further studies are important to continue with the advancement of therapy. ■

Table 1. Data of treated population

		P1	P2	P3	P4
Age at the time of first consultation		15 months	7 months	7 years and 2 months	18 months
Reason for consultation at the Department of Endocrinology		Altered thyroid profile, which was requested due to developmental delay.	Altered thyroid profile, which was requested due to malnutrition.	Diagnosis of central hypothyroidism in another facility. Elevated T3 while receiving levothyroxine, which normalizes when discontinued.	Altered thyroid profile, which was requested due to developmental delay .
Follow-up duration		3 years and 6 months	2 years and 6 months	1 year and 1 month	7 months
Clinical manifestations	Hypotonia	X	X	X	X
	Low muscle mass			X	
	Appendicular spasticity	X	X	X	X
	Overall developmental delay	X	X	X	X
	Difficulty feeding		X	X	
	Underweight		X	X	
	Other		Irritability		
Magnetic resonance imaging		Supratentorial white matter hypomyelination	Subcortical white matter hypomyelination	Hypogenesis of the corpus callosum	Pending
Initial lab tests	TSH mIU/mL	5.85 (NV: 0.97–4.35)	2.58 (NV: 0.84–4.31)	0.04 (NV: 0.82–4.74)	4.04 (NV: 0.97–4.35)
	T3 ng/mL	3.3 (NV: 0.29–2.26)	3.19 (NV: 1.03–2.3)	4.7 (NV: 0.99–2.14)	3.56 (NV: 0.29–2.26)
	T4 ug/dL	3.8 (NV: 5.7–13)	5.7 (NV: 5.3–14.3)	10.5 (NV: 5.7–11.5)	5.72 (NV: 5.7–13)
	FT4 ng/dL	0.68 (NV: 0.89–1.93)	0.65 (NV: 0.86–1.9)	1.23 (NV: 0.91–1.91)	0.72 (NV: 0.89–1.93)
	SHBG nmol/L	344 (NV: 19.8–114)	180 (NV: 19.8–114)	360 (NV: 42.9–120) *Receiving levothyroxine	180 (NV: 19.8–114)
Molecular study	Index case	c.511>T p.Arg171Ter	1461delC - c. p.Ile488SerfsTer5	1461delC - c.p.Ile488SerfsTer5	c.64C>T - p.Gln22Ter
		nonsense	hemizygous frameshift	hemizygous frameshift	nonsense
	Mother		heterozygous	mosaic	mosaic
Treatment	Start date	Nov-2019	Jun-2020	Jan-2022	Jun-2022
	Treatment duration	32 months	22 months	6 months	5 months
	Time to T3 normalization		3 months		2 months
	Current dose	22 µg/kg	18 µg/kg	10 µg/kg	26 µg/kg
Lab tests from last control	TSH mUI/ml	4 (NV: 0.97–4.35)	4 (NV: 0.84–4.31)	1.4 (NV: 0.82–4.7)	4.2 (NV: 0.82–4.74))
	T3 ng/mL	2.7 (NV: 0.29–2.26)	2.12 (NV: 1.03–2.3)	1.52 (NV: 0.99–2.14)	2.08 (NV: 0.29–2.26)
	T4 ug/dL	2.4 (NV: 5.7–13)	2.2 (NV: 5.3–14.3)	2.56 (NV: 5.7–11.5)	2.8 (NV: 5.7–13)
	FT4 ng/dL	0.48 (NV: 0.89–1.93)	0.56 (NV: 0.86–1.9)	0.56 (NV: 0.91–1.91)	0.58 (NV: 0.89–1.9)
	SHBG nmol/L	261 (NV: 19.8–114)	180 (NV: 19.8–114)	487 (NV: 42.9–120)	163 (NV: 19.8–114)
Clinical improvement parameters during the last control	Spasticity	X	X	X	X
	Muscle tone	X	X		
	New neurodevelopment milestones	X	X		X
	Weight		X	X	

NV: normal value. TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: tetraiodothyronine or thyroxine; FT4: free thyroxine; SHBG: sex hormone binding globulin.

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