CASE REPORT

DOI: 10.4274/jcrpe.galenos.2023.2023-10-1

J Clin Res Pediatr Endocrinol 2024;16(1):116-122

Impact of Early Intervention with Triiodothyroacetic Acid on Peripheral and Neurodevelopmental Findings in a Boy with MCT8 Deficiency

Yağmur Ünsal[1], Gamze Hayran[2]

[1]Şanlıurfa Training and Research Hospital, Clinic of Pediatric Endocrinology, Şanlıurfa, Turkey
[2]Şanlıurfa Training and Research Hospital, Clinic of Developmental Pediatrics, Şanlıurfa, Turkey

What is already known on this topic?

Thyroid function tests suggestive of central hypothyroidism in a boy with infantile hypotonia should alert the clinician to measure free triiodothyronine (FT3), while monocarboxylate transporter 8 (MCT8) deficiency should be in the differential diagnosis as early recognition and intervention is crucial. T3 and its analogue, Triac are structurally similar. Many commercial total T3 and FT3 assays are shown to cross-react significantly with Triac in a dose-dependent manner. Triac is known to improve clinical and biochemical signs of hyperthyroidism in patients with MCT8 deficiency by 12 months of treatment. However, earlier trials on efficacy of Triac were not designed to detect neurodevelopmental outcomes and age range of the study populations was diverse.

What this study adds?

After one year of Triac treatment, a significant change in neurodevelopmental scores were not recorded in the presented MCT8 deficient patient. However clinical improvement in critical developmental milestones were evident including at six months habituating to objects, recognizing and smiling at his mother, responding to a person's voice by turning his head, raising his face while in prone position and holding his head steady for a few seconds while in sitting position, and at 12 months responding to his name by turning his head, following a person across the room with eyes and head, and holding his head steady for at least 15 seconds. Regression was not observed. Early intervention with disease-modifying treatment, Triac, enables advances in peripheral findings of MCT8 deficiency as well as neurodevelopmental outcomes and may alleviate the risk factors of morbidity and mortality. Unexpectedly high FT3 in a patient receiving Triac should alert the clinician about a possible interference with FT3 when measured by immunoassay. If signs of hyperthyroidism are absent, patients should have their thyroid function test measured by mass spectrometry without a change in dose, keeping cross-reactivity in mind.

Abstract

Monocarboxylate transporter 8 (MCT8) deficiency is a rare genetic disorder characterized by peripheral thyrotoxicosis and severe cognitive and motor disability due to cerebral hypothyroidism. 3,3',5-triiodothyroacetic acid (Triac) was shown to improve peripheral thyrotoxicosis but data on neurodevelopmental outcome are scarce. We present a case of MCT8 deficiency and the experience with Triac focusing on change in neurodevelopmental and peripheral features. A five-month-old boy was referred because of feeding difficulty, central hypotonia and global developmental delay. Despite six months of physiotherapy, physical developmental milestones did not improve, and distal muscle tone was increased. A hemizygous pathogenic variant in *SLC16A2* was found and MCT8 deficiency was confirmed at 19-months. Thyroid stimulating hormone was 2.83 mIU/mL, free thyroxine 6.24 pmol/L (N = 12-22) and free triiodothyronine (FT3) 15.65pmol/L (N = 3.1-6.8). He had tachycardia, blood pressure and transaminases were elevated. Triac was started at 21-months. Two weeks after treatment, FT3 dramatically decreased, steady normal serum FT3 was achieved at 28-months. Assessment of neurodevelopmental milestones and signs of hyperthyroidism were evaluated at baseline, 6 months and 12 months after treatment. Signs of hyperthyroidism were improved by 6 months. Developmental composite scores of Bayley Scales of Infant Developmental 3rd Edition remained the same

Address for Correspondence: Yağmur Ünsal MD, Şanlıurfa Training and Research Hospital, Clinic of Pediatric Endocrinology, Şanlıurfa, Turkey
Phone: +90 536 795 07 60 **E-mail:** yagmurunsal@yahoo.com **ORCID:** orcid.org/0000-0002-9113-8683

Conflict of interest: None declared
Received: 23.10.2023
Accepted: 25.11.2023

but important developmental milestones (head control, recognition of caregiver, response to his name) were attained, regression in the attained milestones were not observed. Initial dose, management protocol for Triac and research into its efficacy on neurodevelopmental signs in MCT8 deficiency are progressing. This case presents evidence that Triac may resolve peripheral thyrotoxicosis successfully and may slow neurodevelopmental regression, while some developmental milestones were achieved after one year of treatment.
Keywords: MCT8 deficiency, Allan-Herndon-Dudley syndrome, triiodothyroacetic acid (Triac), neurodevelopmental outcome, T3 analogue

Introduction

Thyroid hormones (TH) include thyroxine (T4) and triiodothyronine (T3) and are essential for normal physiology, particularly neurodevelopment, and regulation of basal metabolic rate. Precise regulation of intracellular TH signaling by transport of TH across the cell membrane is facilitated by specific hormone transporter proteins, conversion of T4 into T3 or reverse T3 and further degredation into other inactive TH metabolites is regulated by deiodinating enzymes type 1-3, while genomic action of T3 upon binding TH receptors (TR) and, ensures hypothalamus-pituitary-thyroid (HPT) axis homeostasis (1). Monocarboxylate transporter 8 (MCT8), one of these specific membrane transporter proteins, is capable of mediating TH flux through facilitated diffusion (1). While transport of free T3 (fT3) and free T4 (fT4) across the blood-brain-barrier is primarily dependent on MCT8, peripheral tissues rely on other transporters (2,3,4).

Pathogenic variants of *SLC16A2* (located on Xq13.2) that encodes MCT8 cause a rare neurodevelopmental disorder, called MCT8 deficiency or Allan-Herndon-Dudley syndrome (3,4). Multiple hypotheses have been postulated concerning the pathophysiology of the distinct TH fingerprint of elevated serum fT3 concentrations with reduced fT4 and normal thyroid stimulating hormone (TSH) concentrations, hence further studies are warranted (1). It is most likely that impaired TH transport to the central nervous system (CNS) causes the neurodevelopmental findings of severe developmental delay, central hypotonia from birth, and dystonia, as well as hypertonia after the first year of life, while chronic peripheral thyrotoxicosis precipitates tachycardia, muscle wasting, hypermetabolism and progressive weight loss (5,6). The disease has been associated with significant morbidity and mortality (5,6).

Theraputic options for MCT8 deficiency are rather limited but one of these, the natural TH metabolite 3,3',5-triiodothyroacetic acid or tiratricol (Triac), is a suitable candidate. Firstly, as its cellular transport is not dependent on MCT8, it inhibits TSH production and secretion lowering endogenous TH production (7). Secondly it binds to TR1 with a similar affinity to T3 and has a 3- to 6-fold higher affinity than T3 for TR and TR, yet has relatively low thyromimetic activity in peripheral tissues (8). In addition to its effect on the HPT axis, it has been reported that the thyromimetic effect of Triac, at an equal TSH suppressive dose, are at least as potent as those of T4 in most peripheral organs such as liver and skeletal muscle (9). Aiming to resolve both hypothyroidism in the CNS and peripheral hyperthyroidism, clinical studies have indicated that Triac is effective and safe in pediatric patients with MCT8 deficiency when treating peripheral thyrotoxicosis (10). However evaluation of neurocognitive outcome in Triac treated pediatric patients with MCT8 deficiency, especially before completion of brain development and myelination, are lacking (10).

Guiding treatment for rare diseases such as MCT8 deficiency is challenging, as uniform, systematic collection of long-term data are lacking. This case report describes a case of MCT8 deficiency treated with Triac, providing additional clinical evidence about the effect of Triac on peripheral as well as neurocognitive features, while neurodevelopment and myelination continued.

Case Report

A five-month-old boy was referred to the neurology clinic for feeding difficulty, hypotonia and developmental delay. He was born via Cesarian section due to oligohydramnios at 38 weeks of gestation with a birth weight of 2800 grams [-1.1 standard deviation score (SDS)] and a head circumference of 34 cm (-0.5 SDS). He was discharged after a routine follow-up of two days and passed the neonatal hearing test as well as newborn screening tests. He was the sixth child of a healthy Caucasian couple who were second cousins. He had three healthy sisters and two brothers; relevant family history was absent.

Initial physical examination at five months revealed central hypotonia and developmental delay. He was unable to hold his head, smile or make eye contact. Serum TSH was 2.3 mIU/mL with a low fT4 of 10 pmol/L (N = 12-22) (Table 1). Laboratory investigation and metabolic tests were otherwise normal (Table 2). Cranial magnetic resonance imaging revealed hypoplasia of the corpus callosum, and was consistent with delayed myelination. Thyroid function tests suggestive of central hypothyroidism were not present and neurologic follow-up and physiotherapy were implemented. Despite six months of physiotherapy, there was no improvement in physical developmental

milestones and distal muscle tone was increased. Clinical exome sequencing conducted at 12 months for the etiologic investigation of the hypotonic infant revealed a *de novo* novel, hemizygous pathogenic variant (c.430 + 1G > C chrX: 73641903) in *SLC16A2* and MCT8 deficiency was diagnosed (11). The 19-months old patient was then referred to the endocrinology department.

On physical examination, he was underweight (8.1 kg, -2.9 SDS) but his length was 80 cm (-1.3 SDS). Bitemporal narrowing and prominent ears were evident. He was unable to hold his head, smile or make eye contact. Although he had axial hypotonia, deep tendon reflexes were hyperactive and hypertonia in the extremities was evident. Resting tachycardia (148 bpm, 90th-99th percentile) was noted, systolic blood pressure [100/50 mmHg (92nd/84th percentile)]

Table 1. Change in clinical and biochemical signs of MCT8 deficiency on admission (19-months-old), baseline (21-months-old), 6 months after Triac (27-months-old) and 12 months after Triac (33-months-old)

	On admission	Baseline	6 months*	12 months*	Normal range
Auxologic measurements					
Weight (kg)	8.1	8.4	10	11.2	
Weight SDS	-2.9	-2.9	-2.1	-1.8	
Length (cm)	80	82	86	90.2	
Length SDS	-1.3	-1.2	-1.2	-1.1	
Weight for length SDS	-3.2	-3.2	-2.2	-2.1	
Clinical signs of hyperthyroidism					
Resting heart rate (bpm) (percentile)	148 (90th-99th)	150 (90th-99th)	103 (25th-50th)	95 (25th)	
Systolic blood pressure (mmHg)/(percentile)	100 (92nd)	100 (91st)	86 (46th)	90 (56th)	
Diastolic blood pressure (mmHg)/(percentile)	50 (84th)	60 (97th)	54 (87th)	52 (79th)	
Thyroid function tests					
TSH (mIU/mL)	2.83	0.8	0.9	0.7	0.27-4.2
Free T4 (pmol/L)	6.24	5.7	4.4	3.1	12-22
Free T3 (pmol/L)	15.65	11.7	10.9	7.5	3.1-6.8
Laboratory signs of hyperthyroidism					
CK (U/L)	87	168	47	66	< 90
Total cholesterol (mg/dL)	NA	124.7	111.4	128.2	< 170

*Represents time spent from initiation of Triac.
bpm: beats per minute, CK: creatinine kinase, SDS: standard deviation score, MCT8: monocarboxylate transporter 8, TSH: thyroid stimulating hormone

Table 2. Laboratory investigations on admission (19-months-old), baseline (21-months-old), 6 months after Triac (27-months-old) and 12 months after Triac (33-months-old)

	On admission	Baseline	6 months*	12 months*	Normal range
Hemoglobin (g/dL)	11.0	10.8	11.5	10.3	10.7-14.7
Leukocyte (10^3 µ/L)	7.23	7.67	12.8	4.93	7-17.7
Thrombocyte (10^3 µ/L)	311	255	368	277	150-450
BUN (mg/dL)	19.9	23.6	8.9	26.2	5-18
Creatinine (mg/dL)	0.3	0.3	0.2	0.4	0.16-0.39
Albumin (g/L)	3.8	4.1	3.9	4.1	3.8-5.4
Sodium (mEq/L)	136	136.0	136.0	144.0	136.0-146.0
Potassium (mg/dL)	4.3	4.3	4.6	3.9	4.1-5.3
Calcium (mg/dL)	10.2	10.2	9.8	9.5	8.8-10.9
Phosphate (mg/dL)	4.8	4.7	1.8	4.4	3.9-7.7
ALP (U/L)	179	168	232	220	100-450
ALT (U/L)	168	101	77	68	0-40
AST (U/L)	101	130	102	75	0-40
GGT (U/L)	65	55	66	39	0-40

*Represents time spent from initiation of Triac.
BUN: blood urea nitrogen, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase

was elevated, but systems were otherwise normal. Endocrine evaluation revealed normal TSH (2.83 mIU/mL), low fT4 (6.24 pmol/L N = 12-22) and increased fT3 (15.65 pmol/L N = 3.1-6.8) (Table 1) with an elevated T3/T4 ratio over 0.75. Laboratory evaluation for signs of peripheral thyrotoxicosis revealed slightly abnormal liver function tests (alanine aminotransferase 168 U/L and aspartate aminotransferase 101 U/L) and creatine kinase (CK) (Tables 1, 2). Total cholesterol was normal (Table 1). Electrocardiography (ECG) and transthoracic echocardiography (TTE) did not reveal any pathological finding.

Triac Treatment

As soon as the diagnosis of MCT8 deficiency was confirmed and required local approvals were completed, Triac (Emcitate tablets, 350 mcg, Egetis Therapeutics, Klara Norra Kyrogata 26, Stockholm, Sweden) was started at 21 months via the compassionate use programme. TH were measured using an immunoassay (Roche Modular E170 Immunology Analyzer, Hague Rd, Indianopolis, USA). The patient was assessed for clinical and biochemical signs of peripheral hyperthyroidism and neurodevelopmental changes, at baseline, 6 months and 12 months after start of treatment with Triac.

Thyroid Function Tests

After an initial dose of 175 mcg/day of Triac, fT3 dramatically decreased to 4.7 nmol/L (N = 3.1-6.8) within two weeks. However it subsequently increased again (Figure 1). An individualized dose escalation of 175 mcg steps with a goal of attaining normal serum fT3 concentration was conducted using frequent clinic visits. After an initial decrease, despite increasing Triac to 1125 mcg/day (twice a day, po), fT3 levels remained high at 8.6-13.1 pmol/L (N = 3.1-6.8) (Figure 1).

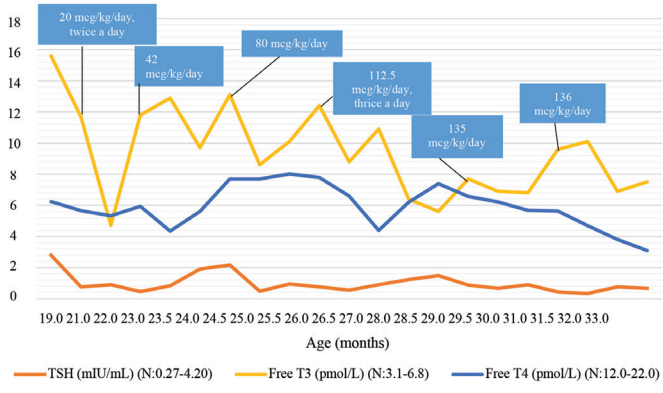

Figure 1. Change in TSH, free T4 and free T3 after initiating Triac when the patient was 21 months old. Blue boxes represent daily Triac dose per kilogram, the dosing regimen was mentioned at the time of change and was continued thereafter

TSH: thyroid stimulating hormone

After identifying adherence issues where there have been times where the patient did not receive treatment for 3-4 consecutive days, the patient was hospitalized for a short time-period and Triac dose adjustment was made. Following discharge, clinic visits included empty Triac box counts in order to try and resolve the adherence issue.

Despite precise treatment, extremely high fT3 (45.1 and 39 pmol/L at the sixth and ninth months of treatment, respectively) were observerd. Concomitant TSH was 0.96 mIU/mL and fT4 5.13 pmol/L (N = 12-22). This unexpected, drastic increase was presumed to be explained by molecular interference of Triac and fT3 in the biochemical analysis, and Triac dose was not changed. In support of this treatment decision, clinical signs of hyperthyroidism were absent and fT3 was near-normal two days after this elevated level (Figure 1). By seven months of treatment, the goal of attaining normal serum fT3 was achieved continuously. Since then, fT3 levels have been high-normal. After one year of treatment, fT3 concentration was reduced to 7.5 pmol/L (N = 3.1-6.8), serum fT4 was 3.09 pmol/L (N = 12-22) and daily dose of Triac was increased eventually to 1500 mcg/day (133 mcg/kg/day) three times a day, po.

Signs of Hyperthyroidism

He was fed orally prior to treatment and continued with oral feedings as consent for tube feeding was not provided by his family. Caloric consumption was adequate for requirements according to age, gender and body weight both prior to and after the treatment. Without change in caloric consumption per kilograms, body weight for length SDS have improved significantly at six months of treatment which was sustained until 12 months afte start of Triac. Resting heart rate measured by ECG, were compared using age adjusted percentile curves and found to be decreased by six months and this was maintained until 12 months (Table 1) (12). Systolic and diastolic blood pressure was decreased and stabilized by 12 months of Triac treatment (Table 1). ECG and TTE were repeated at 12 months and did not reveal any accompanying pathology. Mild elevation in ALT, AST and CK improved within six months (Tables 1, 2). Sex hormone binding globulin could not be measured as it was not available in our clinic.

Problems with adherence to treatment were mainly linked to socioeconomic factors, as well as the populous family structure. No drug related toxicity, need for dose reduction or adverse effect was encountered. He developed upper respiratory tract infection three times during this period which was not attributed to Triac, since they resolved while drug was continued.

Neurodevelopmental Evaluation

Comprehensive developmental assessment was performed by a developmental-behavioral pediatrician. Detailed developmental history and a standardized assessment tool, Bayley Scales of Infant Development 3rd Edition (BSID-III) were used (13). At baseline, prior to Triac (21- months-old) developmental history revealed that developmental milestones were not achieved and BSID-III composite scores for cognitive [55; 95% confidence interval (CI): 51-67], language (47; 95% CI: 43-58) and motor (46; 95% CI: 43-58) evaluation were below two SDS for age.

At six months of Triac treatment, BSID-III composite scores remained below two SDS for age but he started to habituate to objects, recognize and smile at his mother, respond to a person's voice by turning his head, raise his face while in prone position and hold his head steady for a few seconds while in sitting position. As dystonia remained prominent at six months of treatment, oral baclofen was started to ease pain and increase quality of life. At 12 months, BSID-III composite scores remained unchanged (below two SDS for age), but he started to respond to his name by turning his head, follow a person across the room with eyes and head, and hold his head steady for at least 15 seconds and dystonia was improved. Although an improvement in developmental composite scores during follow-up assessments were not observed, an improvement in critical developmental milestones were present. Regression was not observed in any developmental domain.

Discussion

This case highlights the presentation of the extremely rare MCT8 deficiency, which may be missed. Thyroid function tests suggestive of central hypothyroidism in a boy with infantile hypotonia should alert the clinician to measure fT3, and MCT8 deficiency should be in the differential diagnosis, as early recognition and intervention is crucial. This case contributes both peripheral clinical and neurodevelopmental outcomes after one year of Triac treatment and before completion of neurodevelopment and myelination to the literature.

Thorough evaluation of disease presentation and the phenotypic spectrum in MCT8 deficiency, especially concerning neurodevelopmental features, are sparse and disease awareness may be inadequate (6). Data about neurocognitive phenotype and neurodevelopmental outcome are not uniformly collected (5). A natural course study previously described that all patients with MCT8 deficiency had moderate-to-severe intellectual disability with severe delay in motor and language domains (6). At a median age of 7.4 years (0.4-66.8 years), median composite scores in BSID-III were well-below 12 months in all tested sub-domains. In severely affected patients, none of the scores in developmental domains improved with age, while fine motor skills even showed regression.

Triac was shown to decrease serum fT3 concentrations, substantially improving clinical and biochemical signs of hyperthyroidism by six months, which was sustained until 12 months, as in the presented case (5,10). Although Groeneweg et al. (10) reported that 77% of their patients achieved normal serum T3 concentrations by four months of treatment, this only occurred after seven months of treatment in the present case. It may have taken longer in the current patient due to poor adherence, especially in the first months of treatment. The Triac dose (136 mcg/kg/day) required to normalize fT3 was much higher in the present case than previously described (23-48 mcg/kg/day) (8,10). As clinical signs of peripheral hypothyroidism were not observed, it was deduced that this dose compensated the reduction in fT4. While Triac was administered twice or thrice a day in previous studies, we observed that the normal range of fT3 was best maintained if Triac was administered thrice a day (5,10). In addition, clinical signs of hyperthyroidism resolved as progressive deterioration of bodyweight was prevented, and an advancement in bodyweight and length with normal heart rate and blood pressure were accomplished.

Since reduction of fT3 is the aim of successful Triac treatment in MCT8 deficiency, accurate fT3 measurement is crucial for dose adjustment. As T3 and Triac are structurally similar, many commercial total T3 and fT3 assays have been reported to cross-react significantly with Triac in a dose-dependent manner (14). To the best of our knowledge, this is the first clinical case report to address and explain this issue in detail. Chan et al. (14) suggested that patients using Triac should have their T3 hormone monitored using alternative methodologies, such as mass spectrometry. However, as mass spectrometric measurement of thyroid function tests is not available in most institutions such as ours, we propose that MCT8 deficient patients on Triac with unexpected high measurements of fT3 should have their thyroid function test measured by mass spectrometry only if signs of hyperthyroidism are absent.

Previous studies into the efficacy of Triac have demonstrated a notable decrease in serum fT4 (5,6,10). It was speculated that the thyromimetic effect of Triac on peripheral tissues compensated for the reduction in fT4 (10). Since then, the effect of low T4 on neurocognitive function has been a debate and have yet to be clarified. Bárez-López et al. (15) studied this dilemma on MCT8KO mice and concluded that

hypothyroxinemia in the CNS due to low plasma T4 levels may potentially be harmful if this effect was not attenuated by thyromimetic effect of Triac. However, there are some limitations to that study. Firstly, MCT8KO mice' brains were shown to be mildly hypothyroid lacking overt neurological abnormalities and the results of this model on neurocognitive phenotype is not transferrable to humans (1,16). Secondly, the dose of Triac was on the lower side of the recommended dose for humans and dose adjustment was not performed. More recently, MCT8/OATP1C1 DKO mice were validated to be a valuable model organism for the preclinical evaluation of drugs as they exhibit both peripheral and neurocognitive phenotype (17). Previous studies starting Triac as early as possible on the first day of life in MCT8/OATP1C1 DKO mice report a recuperated neuromotor phenotype (18).

Earlier clinical trials on the efficacy of Triac were not designed to detect neurodevelopmental outcomes and study populations' age was very variable (5,10). Although an improvement in developmental composite scores during follow-up were not observed in the present case, clinical improvement in critical developmental milestones were evident, and regression was prevented. At twelve months of treatment, our patient started to respond to his name by turning his head, follow a person across the room with eyes and head, and hold his head steady for at least 15 seconds. Head control, which was previously presented as a marker of improved neurodevelopment and a significant indicator of increased survival rate, was achieved (6). Oral baclofen, a GABA-B agonist was administered for dystonia and related pain. Although the effect of oral baclofen on patients with MCT8 deficiency has not previoulsy been studied, considering it is the most often used oral drug for dystonic cerebral palsy with low efficacy and no known effect on neurodevelopment, oral baclofen was presumed not to have an impact on developmental milestones (19).

Given the insufficiency of data about the effectiveness of Triac in MCT8 deficiency for optimal neurocognitive and neurodevelopmental outcome, larger studies of international collaborative networks for this rare disorder are needed (5). This case presents additional evidence that early diagnosis, while neurodevelopment and myelination continue, is of utmost importance. Early initiation of disease-modifying treatment, Triac, may prevent regression and establish progress in neurodevelopmental milestones while decreasing mortality by its peripheral effects.

Groeneweg et al. (6) reported that overall survival of patients with MCT8 deficiency was greatly diminished with 30% mortality during childhood. Being underweight was associated with increased risk of infections while achieving normal bodyweight was shown to increase median survival from 30.3 to 71 years; however cause of death was unclear in 46.9% (6). It may be hypothesized that mortality due to these unclear reasons and sudden death may be due to a cardiac cause since prevalence of premature atrial and ventricular contractions are high (6). Holter evaluation was not performed in our patient, but cardiac arrythmia was not observed on ECG and improvements in bodyweight, heart rate and blood pressure, as well as markers of thyroid action, may suggest that Triac may decrease the risk factors for mortality in MCT8 deficiency, especially considering the proposals of Groeneweg et al. (6).

Conclusion

The importance of this case is that it reports an in-depth clinical experience with an infant with MCT8 deficiency who was administered Triac. It is essential to keep in mind that fT3 and Triac may cross react if measured with immunoassay in MCT8 deficient patients who are on Triac and thyroid function test should be measured using mass spectrometry if available and if unexpectedly high measurements of fT3 are encountered. Consensus on starting dose of Triac, management protocol and research for its efficacy on central and peripheral signs of MCT8 deficiency are still progressing. This case provides additional evidence that Triac may successfully restore peripheral findings of MCT8 deficiency after one year of treatment. Although a significant change in neurodevelopmental scores were not recorded, neurodevelopmental regression was decelerated and important developmental milestones were achieved. These advances in both peripheral findings of MCT8 deficiency, as well as neurodevelopmental outcomes, may alleviate the risk factors of morbidity as well as mortality.

Acknowledgments

The authors would like to thank Süleyman Atar, MD of Pediatric Genetics Clinic for their contribution regarding the analysis of clinical exome sequencing and Professor Zeynep Alev Özön, MD for reviewing our work and providing important intellectual content. We are appreciative of our patient's family for providing consent for publication of this work.

Ethics

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: Yağmur Ünsal, Gamze Hayran, Concept: Yağmur Ünsal, Design: Yağmur Ünsal, Data Collection or Processing: Yağmur Ünsal, Gamze

Hayran, Analysis or Interpretation: Yağmur Ünsal, Gamze Hayran, Literature Search: Yağmur Ünsal, Writing: Yağmur Ünsal, Gamze Hayran.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. van Geest FS, Gunhanlar N, Groeneweg S, Visser WE. Monocarboxylate Transporter 8 Deficiency: From Pathophysiological Understanding to Therapy Development. Front Endocrinol (Lausanne) 2021;12:723750.
2. Ceballos A, Belinchon MM, Sanchez-Mendoza E, Grijota-Martinez C, Dumitrescu AM, Refetoff S, Morte B, Bernal J. Importance of monocarboxylate transporter 8 for the blood-brain barrier-dependent availability of 3,5,3'-triiodo-L-thyronine. Endocrinology 2009;150:2491-2496. Epub 2009 Jan 15
3. Chen X, Liu L, Zeng C. A novel variant in SLC16A2 associated with typical Allan-Herndon-Dudley syndrome: a case report. BMC Pediatr 2022;22:180.
4. Visser WE, Vrijmoeth P, Visser FE, Arts WF, van Toor H, Visser TJ. Identification, functional analysis, prevalence and treatment of monocarboxylate transporter 8 (MCT8) mutations in a cohort of adult patients with mental retardation. Clin Endocrinol (Oxf) 2013;78:310-315.
5. van Geest FS, Groeneweg S, van den Akker ELT, Bacos I, Barca D, van den Berg SAA, Bertini E, Brunner D, Brunetti-Pierri N, Cappa M, Cappuccio G, Chatterjee K, Chesover AD, Christian P, Coutant R, Craiu D, Crock P, Dewey C, Dica A, Dimitri P, Dubey R, Enderli A, Fairchild J, Gallichan J, Garibaldi LR, George B, Hackenberg A, Heinrich B, Huynh T, Kłosowska A, Lawson-Yuen A, Linder-Lucht M, Lyons G, Monti Lora F, Moran C, Müller KE, Paone L, Paul PG, Polak M, Porta F, Reinauer C, de Rijke YB, Seckold R, Menevşe TS, Simm P, Simon A, Spada M, Stoupa A, Szeifert L, Tonduti D, van Toor H, Turan S, Vanderniet J, de Waart M, van der Wal R, van der Walt A, van Wermeskerken AM, Wierzba J, Zibordi F, Zung A, Peeters RP, Visser WE. Long-Term Efficacy of T3 Analogue Triac in Children and Adults With MCT8 Deficiency: A Real-Life Retrospective Cohort Study. J Clin Endocrinol Metab 2022;107:1136-1147.
6. Groeneweg S, van Geest FS, Abacı A, Alcantud A, Ambegaonkar GP, Armour CM, Bakhtiani P, Barca D, Bertini ES, van Beynum IM, Brunetti-Pierri N, Bugiani M, Cappa M, Cappuccio G, Castellotti B, Castiglioni C, Chatterjee K, de Coo IFM, Coutant R, Craiu D, Crock P, DeGoede C, Demir K, Dica A, Dimitri P, Dolcetta-Capuzzo A, Dremmen MHG, Dubey R, Enderli A, Fairchild J, Gallichan J, George B, Gevers EF, Hackenberg A, Halász Z, Heinrich B, Huynh T, Kłosowska A, van der Knaap MS, van der Knoop MM, Konrad D, Koolen DA, Krude H, Lawson-Yuen A, Lebl J, Linder-Lucht M, Lorea CF, Lourenço CM, Lunsing RJ, Lyons G, Malikova J, Mancilla EE, McGowan A, Mericq V, Lora FM, Moran C, Müller KE, Oliver-Petit I, Paone L, Paul PG, Polak M, Porta F, Poswar FO, Reinauer C, Rozenkova K, Menevse TS, Simm P, Simon A, Singh Y, Spada M, van der Spek J, Stals MAM, Stoupa A, Subramanian GM, Tonduti D, Turan S, den Uil CA, Vanderniet J, van der Walt A, Wémeau JL, Wierzba J, de Wit MY, Wolf NI, Wurm M, Zibordi F, Zung A, Zwaveling-Soonawala N, Visser WE. Disease characteristics of MCT8 deficiency: an international, retrospective, multicentre cohort study. Lancet Diabetes Endocrinol 2020;8:594-605. doi: 10.1016/S2213-8587(20)30153-4. Erratum in: Lancet Diabetes Endocrinol 2020;8:594-605. Erratum in: Lancet Diabetes Endocrinol 2022;10:e7.
7. Senese R, Cioffi F, Petito G, Goglia F, Lanni A. Thyroid hormone metabolites and analogues. Endocrine 2019;66:105-114. Epub 2019 Jul 29
8. Groeneweg S, Peeters RP, Visser TJ, Visser WE. Triiodothyroacetic acid in health and disease. J Endocrinol 2017;234:99-121. Epub 2017 Jun 2
9. Sherman SI, Ringel MD, Smith MJ, Kopelen HA, Zoghbi WA, Ladenson PW. Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyroxine. J Clin Endocrinol Metab 1997;82:2153-2158.
10. Groeneweg S, Peeters RP, Moran C, Stoupa A, Auriol F, Tonduti D, Dica A, Paone L, Rozenkova K, Malikova J, van der Walt A, de Coo IFM, McGowan A, Lyons G, Aarsen FK, Barca D, van Beynum IM, van der Knoop MM, Jansen J, Manshande M, Lunsing RJ, Nowak S, den Uil CA, Zillikens MC, Visser FE, Vrijmoeth P, de Wit MCY, Wolf NI, Zandstra A, Ambegaonkar G, Singh Y, de Rijke YB, Medici M, Bertini ES, Depoorter S, Lebl J, Cappa M, De Meirleir L, Krude H, Craiu D, Zibordi F, Oliver Petit I, Polak M, Chatterjee K, Visser TJ, Visser WE. 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;7:695-706. Epub 2019 Jul 31
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-424. Epub 2015 Mar 5
12. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, Tarassenko L, Mant D. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377:1011-1018.
13. Bayley N. Bayley scales of infant and toddler development. 3rd ed. San Antonio: Pearson Education, 2006.
14. Chan SL, Refetoff S, Babic N, Jin M, Garg U, Yeo KJ. Triiodothyroacetic Acid Cross-Reacts With Measurement of Triiodothyronine (T3) on Various Immunoassay Platforms. Am J Clin Pathol 2022;157:156-158.
15. Bárez-López S, Obregon MJ, Martínez-de-Mena R, Bernal J, Guadaño-Ferraz A, Morte B. Effect of Triiodothyroacetic Acid Treatment in Mct8 Deficiency: A Word of Caution. Thyroid 2016;26:618-626. Epub 2016 Feb 3
16. Visser WE, Heuer H, Visser TJ. Triiodothyroacetic Acid Treatment in MCT8 Deficiency: A Word of Nuance. Thyroid 2016;26:615-617.
17. Maity-Kumar G, Ständer L, DeAngelis M, Lee S, Molenaar A, Becker L, Garrett L, Amerie OV, Hoelter SM, Wurst W, Fuchs H, Feuchtinger A, Gailus-Durner V, Garcia-Caceres C, Othman AE, Brockmann C, Schöffling VI, Beiser K, Krude H, Mroz PA, Hofmann S, Tuckermann J, DiMarchi RD, Hrabe de Angelis M, Tschöp MH, Pfluger PT, Müller TD. Validation of Mct8/Oatp1c1 dKO mice as a model organism for the Allan-Herndon-Dudley Syndrome. Mol Metab 2022;66:101616. Epub 2022 Oct 18
18. Kersseboom S, Horn S, Visser WE, Chen J, Friesema EC, Vaurs-Barrière C, Peeters RP, Heuer H, Visser TJ. In vitro and mouse studies supporting therapeutic utility of triiodothyroacetic acid in MCT8 deficiency. Mol Endocrinol 2014;28:1961-1970.
19. Monbaliu E, Himmelmann K, Lin JP, Ortibus E, Bonouvrié L, Feys H, Vermeulen RJ, Dan B. Clinical presentation and management of dyskinetic cerebral palsy. Lancet Neurol 2017;16:741-749.