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

Ünsal Y and Hayran G. The Impact of Triac on MCT8 Deficiency

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What is known
- 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 included 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 population was diverse.

What's new
- After one year of Triac treatment, a significant change in neurodevelopmental scores were not recorded in our MCT8 deficient patient.
- However clinical improvement in critical developmental milestones (6th month: habituating to objects, crying, 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, 12th month: 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) were evident, and regression was not observed.
- Early intervention with disease-modifying treatment, (i.e. Triac) enables advancement 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, 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. Herein a case of MCT8 deficiency and the experience with Triac focusing on change in neurodevelopmental and peripheral features are being presented. Five-month-old boy was referred for feeding difficulty, central hypotonia starting from birth, and dystonia as well as hypertonia after the first year of life) while chronic peripheral thyrotoxicosis successfully and may slow neurodevelopmental regression, while some developmental milestones could be achieved after one year of treatment.

Keywords: MCT8 deficiency, Allan-Herndon-Dudley syndrome, triiodothyroacetic acid (Triac), neurodevelopmental outcome, T3 analogue

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23.10.2023
25.11.2023
Published: 06.12.2023

Introduction
Thyroid hormones (TH; thyroxine (T4) and triiodothyronine (T3)) are essential for normal physiology, particularly neurodevelopment, and regulation of basal metabolic rate. Precise regulation of intracellular thyroid hormone signaling by transport of TH across the cell membrane facilitated by specific hormone transporter proteins, conversion of T4 into T3 or reverse T3 and further degradation into other inactive TH metabolites by deiodinating enzymes type 1-3 (DIO1-3) and genomic action of T3 upon binding thyroid hormone receptor (TR) α and β, 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 blood-brain-barrier is primarily dependent on MCT8, peripheral tissues rely on other transporters (2-4).

Pathogenic variants of SLC16A2 (located on Xq13.2) encoding MCT8, cause a rare neurodevelopmental disorder; MCT8 deficiency also known as Allan-Herndon-Dudley syndrome (3). Multiple hypothesis have been postulated on the pathophysiology of distinct TH fingerprint (elevated serum FT3 concentrations with reduced FT4, and normal TSH concentrations) hence further studies are warranted (1). It is most likely that impaired TH transport to the central nervous system (CNS) causes neurodevelopmental findings (severe developmental delay, central hypotonia starting from birth, and dystonia as well as hypertonria 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).

Therapeutic options for MCT8 deficiency are rather limited of which, 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 thyroid hormone production (7). Secondly it binds TTR and T4 with a similar affinity as T3 and a 3- to 6-fold higher affinity than T3 to TRβ1 and TRβ2 yet has relatively low thyromimetic activity in peripheral tissues (8). In addition to its effect on T4, 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 hypothroidism in CNS and peripheral hyperthyroidism, clinical studies indicate that Triac is effective and safe in pediatric patients with MCT8 deficiency when treating peripheral thyrotoxicosis (10). However, evaluation of neurocognitive outcome in pediatric patients, especially before completion of brain development and myelination are lacking (10).

Guiding treatment for rare diseases like MCT8 deficiency is challenging as uniform, systematic collection of long-term data are lacking. Here, a rare case of MCT8 deficiency treated with Triac is being presented, broadening data on its effect on clinical peripheral as well as neurocognitive features while neurodevelopment and myelination continues.

**Case Presentation**

A five-month-old boy was consulted 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 SDS) and a head circumference of 34 cm (-0.5 SDS). He was discharged after a routine follow-up of two days, passed hearing test as well as newborn screening tests. He was the sixth child of a healthy Caucasian couple who were 24th cousins. He had three healthy sisters and two brothers; relevant family history was absent.

Initial physical examination at five months revealed hypothyroidism and developmental delay. He was unable to hold his head, smile or make eye contact. Serum TSH was 2.3 mU/mL with a low FT4 of 10 pmol/L (N:12-22). Laboratory investigation and metabolic tests were normal otherwise (Table 2). Cranial magnetic resonance imaging revealed hypoplasia of corpus callosum, and was consistent with delayed myelination. Thyroid function tests suggestive of central hypothroidism were not noticed and neurologic follow-up and physiotherapy were implemented. Despite 6 months of physiotherapy, there was no improvement in physical developmental milestones and distal muscle tone was increased. Clinical exome sequencing conducted for etiologic investigation of hypotonic infant revealed a novel hemizygous pathogenic variant c.430+1G>C chrX: 73641903 in SLC16A2, MCT8 deficiency was diagnosed (11). In the 19-months old patient was then referred to endocrinology department.

On physical examination, he was underweight (8.1 kg, -2.9 SDS), 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 hypertension in the extremities was evident. Resting tachycardia (140 inspirations/min) was noted, systolic blood pressure (100-50 mmHg (92±48±42)) was elevated, systems were normal otherwise. Endocrine evaluation revealed normal TSH (2.83 mU/mL), low FT4 (6.24 pmol/L N:12-22) and increased FT3 (15.65 pmol/L N:11-6.8) (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 (ALT) 168 U/L, aspartate aminotransferase (AST) 101 U/L) and creatine kinase (CK) (Table 1, Table 2). Total cholesterol was normal (Table 1). Electrocardiography (ECG) and transthoracic echocardiography (TTE) did not reveal any pathological finding.

### Thyroid function tests

After an initial dose of 175 mcg/day of Triac, FT3 dramatically decreased to 4.7 pmol/L (N:3.1-6.8) in two weeks. However it increased later (Figure 1). An individualized dose escalation at 17 mcg every 2 weeks with a goal of attaining normal serum FT3 concentration (N: 3.1-6.8 pmol/L) was conducted with frequent clinic visits. After numerous decrease, despite increasing Triac to 1125 mcg/day (two times a day, po), FT3 levels were still high (8.6-13.1 pmol/L (N:3.1-6.8)) (Figure 1). After realization of 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, clinical signs of thyrotoxicosis were absent and empty Triac box counts to omit the issue. Despite precise treatment, extremely high FT3 (45.1 and 39 pmol/L; 6th and 9th month of treatment, respectively) measurements were observed. 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, and Triac dose was not changed. Supporting this, clinical signs of hyperthyroidism was absent and FT4 was near normal two days after this elevated level (Figure 1). By 7 months of treatment, the goal of attaining normal serum FT3 was achieved continuously. Since then, FT3 levels have been high-normal. On 12th month 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 was maintained 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 6 months which was sustained until 12 months. Resting heart rate measured by ECG, were compared using age adjusted percentile curves and found to be decreased by 6 months, this change was maintained until 12 months (Table 1) (12). Systolic and diastolic blood pressure was decreased and stabilized until 12 months (Table 1). ECG and TTE were repeated at 12 months and did not reveal any accompanying pathology. Mild elevation in ALT, AST and CK ameliorated within 6 months (Table 1, Table 2). Sex hormone binding globulin could not be measured as it was not available in our clinic.

Problems of adherence to treatment were mainly linked to socioeconomic factors as well as 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% CI: 51-67), language (47; 95% CI: 43-58) and motor (46; 95% CI: 43-58) evaluation were below two SDS for age. At 6 months, 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 was prominent at 6th 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...
Discussion
This case underlines the presentation of MCT8 deficiency that 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. Contribution of this paper is that it presents both peripheral clinical and neurodevelopmental outcomes after one year of Triac treatment before completion of neurodevelopment and myelination. Meticulously written clinical insight to MCT8 deficiency and follow-up during Triac treatment is expected to be of great value for similar cases to come.

Thorough evaluation of disease presentation and phenotypic spectrum in MCT8 deficiency, especially on neurodevelopmental features are sparse and disease awareness may be inadequate (6). Data on 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 abnormalities and results of this model on neurocognitive phenotype is not reproducible 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 portray both peripheral and neurocognitive phenotype (17). Previous studies starting Triac as early as possible (the first day of life) in MCT8/OATP1C1 DKO mice also demonstrated a noticeable decrease in serum FT4 (6, 10). It was speculated that thyromimetic effect of Triac on peripheral tissues compensated the reduction in FT4 (10). Since then, the effect of low T4 on neurocognitive function has been a debate and not been clarified. Lopez et al. studied this dilemma on MCT8KO mice and concluded that hypothyroxinemia in CNS due to low plasma T4 levels may potentially be harmful if this effect was not attenuated by thyromimetic effect of Triac (15). However, there are some limitations to that study. Firstly, MCT8KO mice’ brains were shown to be mildly hypothyroid lacking overt neurological abnormalities and results of this model on neurocognitive phenotype is not reproducible to humans (1) (16). Secondly, the dose of Triac was significantly with Triac in a dose-dependent manner (14). To our knowledge, this is the first clinical report to address and explain this issue in detail. Chang et al. suggested that patients using Triac should have their T3 hormone monitored by alternative methodology, such as mass spectrometry (14). However, as mass spectrometric measurement of thyroid function is not available in most of the institutions like 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 if signs of hypothyroidism were absent.

Triac was shown to decrease serum FT3 concentrations substantially improving clinical and biochemical signs of hyperthyroidism by 6 months, which was maintained until 12 months as portrayed in our case (5, 10). Although Groeneweg et al. reported that 77% of the patients achieved normal serum T3 concentrations by 4 months, it was only after seven months of treatment in this case (10). It probably took longer in the current patient due to lack of adherence especially in the first months of treatment. Required Triac dose (133 mcg/kg/day) to normalize FT3 was higher in this 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 normal range of FT3 was best maintained if Triac was administered thrice a day (5, 10). In addition to that, clinical signs of hyperthyroidism were restored 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 its analogue, Triac are structurally similar, many commercial total T3 and FT3 kits were reported to cross-react significantly with Triac in a dose-depending manner (8, 14). To our knowledge, this is the first clinical report to address and explain this issue in detail. Chang et al. suggested that patients using Triac should have their T3 hormone monitored by alternative methodology, such as mass spectrometry (14). However, as mass spectrometric measurement of thyroid function is not available in most of the institutions like 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 if signs of hypothyroidism were absent.

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Funding None declared

Acknowledgments
The authors would like to thank Suleyman Atar, MD of Pediatric Genetics Clinic for their contribution regarding the analysis of clinical exome sequencing and Professor Zeynep Alev Ozon, 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.

References

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)

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<tr>
<th>Auxologic measurements</th>
<th>On admission</th>
<th>Baseline</th>
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<th>12 months*</th>
<th>Normal range</th>
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<td>150 (90th-99th)</td>
<td>103 (25th-50th)</td>
<td>95 (25th)</td>
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<td>Systolic blood pressure (mmHg)(percentile)</td>
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<td>100 (91st)</td>
<td>86 (46th)</td>
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<td>60 (97th)</td>
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<td>Free T3 (pmol/L)</td>
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<td>CK (U/L)</td>
<td>87</td>
<td>168</td>
<td>47</td>
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<td>&lt;90</td>
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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)

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

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<th></th>
<th>On admission</th>
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<th>12 months*</th>
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<td>BUN (mg/dl)</td>
<td>19.9</td>
<td>23.6</td>
<td>8.9</td>
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<td>Potassium (mg/dl)</td>
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<td>Calcium (mg/dl)</td>
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<td>10.2</td>
<td>9.8</td>
<td>9.5</td>
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<td>4.4</td>
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<td>ALP (U/L)</td>
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<td>102</td>
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<td>GGT (U/L)</td>
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<td>55</td>
<td>66</td>
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</table>

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, the dosing regimen was mentioned at the time of change and was continued thereafter.