EDITORIAL

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Diagnosis and Therapy in MCT8 Deficiency: Ongoing Challenges

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Dear Editor,

Monocarboxylate transporter 8 (MCT8) deficiency, or the Allan-Herndon-Dudley syndrome, is a rare neurodevelopmental and metabolic disorder caused by mutations in the *SLC16A2* gene located on the X-chromosome (1,2,3). MCT8 is a crucial thyroid hormone transporter for various tissues, including the brain. Hence, affected boys present with severe neurodevelopmental delay due to cerebral hypothyroidism (1,2,4). Early developmental milestones are often not reached and patients have severe intellectual and motor disability. The endocrine hallmark of MCT8 deficiency is increased serum (free) triiodothyronine (T3) concentrations, with reduced free thyroxine (T4) concentrations and normal to slightly elevated thyroid-stimulating hormone concentrations (4). The elevated (f) T3 concentrations lead to signs of thyrotoxicosis, such as tachycardia and being underweight (4). The disease has been associated with significant morbidity and mortality, with 30% of patients dying in childhood (4).

No approved therapeutic treatments are currently available for patients with MCT8 deficiency. T3-analogue Triac (3,3',5-tri-iodothyroacetic acid, or tiratricol) is not dependent on MCT8 for cellular influx and is, therefore, considered a good candidate for treatment (5,6). The Triac Trial I and subsequent real-world data showed that Triac safely normalizes serum T3 concentrations and ameliorates the symptoms of peripheral thyrotoxicosis in paediatric and adult male patients (7,8). Currently, the Triac Trial II (NCT02396459) is being conducted to explore potential beneficial effects in neurodevelopment in young patients (<30 months), the results of which are expected in 2024/2025. A small multicenter, double-blind, randomized, placebo-controlled trial [ReTRIACt trial (NCT05579327)], aiming to validate the effects of Triac on serum T3 concentrations, is currently recruiting.

In this issue of JCRPE, Ünsal and Hayran (9) present a new case-report of a patient with MCT8 deficiency. Their patient, diagnosed at the age of 14 months, exhibits typical characteristics of MCT8 deficiency, with a first presentation at 5 months of age including central hypotonia, developmental delay and feeding difficulties in combination with borderline normal thyroid function tests. This clinical presentation is in line with the median symptom onset at 4 months and median diagnostic delay of 14 months (10). This supports the claim of the authors that MCT8 deficiency is often overlooked and should be included in the differential diagnosis of young males with developmental delay and hypotonia. Since the "central" component of MCT8 deficiency is the most notable, most patients will be seen primarily by (pediatric) neurologists. Therefore, it is important to raise awareness of MCT8 deficiency in this profession. Moreover, there is large variation in the inclusion of the *SLC16A2* gene in multigene panels across different centers and countries (11), which implies that MCT8 deficiency is not always diagnosed after genetic testing. Consequently, *SLC16A2* should be included in all relevant genetic panels. Additionally, it should be explored whether modification of the newborn screening would allow for diagnosis of MCT8 deficiency immediately after birth (12,13).

In the current case-report, the patient was started on Triac with a maintenance dose of 133 mcg/kg/day (9). To assess neurodevelopmental outcomes, the Bayley Scales of Infant Developmental 3rd Edition (BSID-III) was used

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at baseline and various time points after treatment. No improvements in composite scores were observed after 12-months of treatment, although some improvements in a few developmental milestones were seen, such as improved head control. It is not possible to distinguish whether these changes would occur as part of the natural history or can be attributed to Triac treatment (4). Preclinical studies have indicated the potential of Triac in improving brain outcomes (5,14). Clinical studies sufficiently powered to detect clinically relevant neurodevelopmental changes, like Triac Trial II, might provide clues on potential benefits of early Triac treatment.

The authors report that after start of treatment with Triac, the FT3 values were variable and higher than expected (9), especially since Triac treatment aims to reduce FT3 values. The authors correctly assume that this is likely explained by cross-reactivity of Triac in the used FT3 immuno-assays. In 2022, Chan et al. (15) showed that all immuno-based T3 assays show significant interference with Triac, with assay-specific cross-reactivity profiles. Therefore, it is important to account for interference when interpreting FT3 results, both when unexpected high concentrations are measured as suggested by the authors, and also when T3 concentrations are measured in Triac treated patients. The relatively long time to achieve normal serum T3 values [7 months instead of the earlier reported 4 months by Groeneweg et al. (7)], should therefore also be cautiously interpreted since this was established by using only one immuno-based assay without applying any corrections for cross-reactivity. One way to account for interference is to employ a correction algorithm utilizing immuno-assays with different cross-reactivities towards Triac (7,8). Ultimately, the use of liquid chromatography mass spectrometry should be encouraged, as this allows to accurately distinguish Triac from T3 and prevents misinterpretation of thyroid function tests (15).

Overall, this case-report illustrates multiple challenges in the clinical management of patients with MCT8 deficiency (9). Despite the discovery of patients with mutations in MCT8 20 years ago, many unknowns remain, largely caused by the rarity of this disorder. Hence, like for all rare disorders, international collaboration to collect data in a uniform way on disease features and treatment outcomes is critical to advance diagnosis, management and therapeutic options for patients with MCT8 deficiency.

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Ethics

Authorship Contributions

Concept: Matthijs E.T. Freund, Floor van der Most, W. Edward Visser, Analysis or Interpretation: Matthijs E.T. Freund, Floor van der Most, W. Edward Visser, Literature Search: Matthijs E.T. Freund, Writing: Matthijs E.T. Freund, Floor van der Most, W. Edward Visser.

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