Erasmus MC
University Medical Center Rotterdam

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# Newsletter AHDS/ MCT8 Deficiency

Dear parents, doctors and all who care for people with MCT8 deficiency,

this is the fifth newsletter in our series of newsletters on the AHDS or MCT8 deficiency. In this edition, you can read about the clinical symptoms of MCT8 deficiency and more.

**Progress of Triac Trial I**

The Triac Trial is currently ongoing. Inclusion of new patients in the trial is not possible.

## Clinical symptoms of MCT8 deficiency

As explained in the fourth MCT8 deficiency newsletter, the syndrome is caused by a mutation in the SLC16A2 gene. When this gene contains a pathologic mutation, an incorrect MCT8 protein will be produced.

The MCT8 protein is responsible for the transport of thyroid hormone into the brain (see figure 1A). In MCT8 deficiency, this transport is insufficient. As a consequence, the amount of thyroid hormone (T3) in the brain is low (called *hypo*thyroid state). However, high levels of thyroid hormone are present in the rest of the body (called *hyper*thyroid state). In conclusion, the brain is in a *hypo*thyroid and the rest of the body is in a *hyper*thyroid state (see figure 1B).

Since thyroid hormone is essential for neurological development, the relatively *hypo*thyroid state of the brain results in an abnormal brain development and a broad spectrum of neurological symptoms. The relatively *hyper*thyroid state of the rest of the body causes symptoms of hyperthyroidism in the muscles, heart and abdomen. These symptoms are together called the peripheral symptoms, or the peripheral phenotype (meaning symptoms of organs other than the brain and nerves).

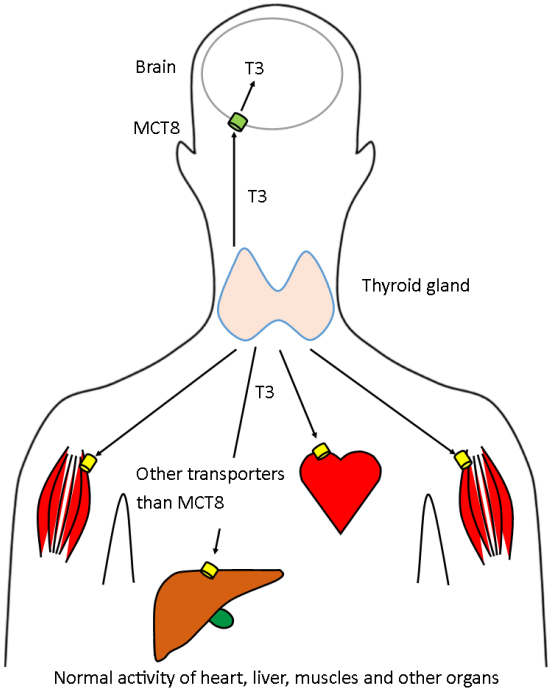


*Figure 1A: Model for normal situation*

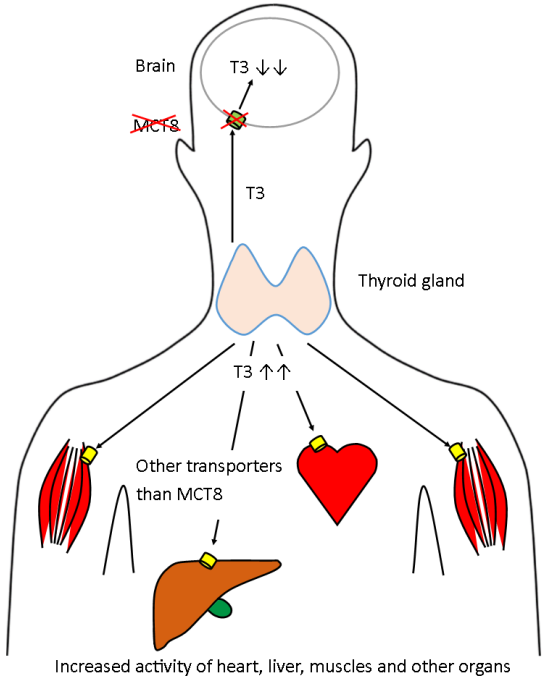


*Figure 1B: Model for MCT8 deficiency*

Green = MCT8; Yellow = other transporters

## Neurological symptoms

Development of the human brain starts early in pregnancy, a few weeks after conception. During development of the brain, connections are made between different brain cells. This process of maturation continues until early adulthood and several aspects highly depend on thyroid hormone.

In MCT8 deficiency, the levels of thyroid hormone are insufficient to stimulate brain development and maturation. As a result, thyroid hormone dependent processes such as the myelination (formation of an isolating sheet around the nerve cells, similar to the plastic isolation sheet around electric wires) of nerve cells and the establishment of connections between the cells in the brain are impaired. These phenomena can be observed on magnetic resonance imaging (MRI) of the brain. The neurological symptoms reflect the delayed development of the brain. Patients with MCT8 deficiency usually present with hypotonia, impaired development of speech and motor skills (such as head balance, sitting independently) and reduced strength of the muscles. During first years of life, patients with MCT8 deficiency may develop dystonia in the extremities (involuntary muscle contractions and spasticity (abnormal tendon reflexes and contractures of joints). Due to this combination, patients are often wheelchair bound.

## Peripheral symptoms

As shown in figure 1B, the level of the active thyroid hormone T3 in the blood is high. The organs in our body that use other transport proteins than MCT8 are exposed to these high T3 concentrations. This leads to symptoms of hyperthyroidism which may include an elevated heart rate (tachycardia), increased energy metabolism and muscle wasting. The combination of these symptoms (often) leads to a very low body weight.

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**Magnetic Resonance Imaging data wanted!**

As explained above, MCT8 deficiency causes a delayed brain development. In order to better understand which processes during brain development are affected in MCT8 deficiency, MRI images may provide valuable information, especially if the images of multiple patients will be analysed and compared to each other. Therefore, we would to ask if you are willing to share brain MRI images. If you are interested, please contact us at s.groeneweg@erasmusmc.nl or f.vangeest@erasmusmc.nl if you have any questions and/or if you are able to send us MRI data.

# In memoriam Prof. Theo Visser

With great disbelieve, we have received the news that Prof. Theo Visser, suddenly passed away. During his carrier, Theo made seminal discoveries to the thyroid hormone transport field. He was among the first to demonstrate that the transport of thyroid hormone into the cell depends on thyroid hormone transporter proteins. Importantly, he discovered MCT8 as thyroid hormone transporter and the mutations in MCT8 leading to the disease. He had major contributions in elucidating the mechanisms behind this disorder and was largely involved in the development of Triac therapy.
We will sincerely miss him as a colleague, a brilliant scientist, a great mentor, and importantly as a dear friend.