Erasmus MC
University Medical Center Rotterdam

Third edition,
April 2016

Newsletter AHDS

Dear parents, doctors and all who care for people with AHDS,

Hereby the third newsletter about the Allan-Herndon-Dudley syndrome and the Triac Trial. In the last newsletter we wrote about the start of the Triac Trial in South Africa and how we were working in several other countries to start the trial there. Since then we have started in Czech Republic, Romania and Belgium. In France, Italy and Germany the first boys will get treated in April. In the United Kingdom and Israel the preparation process is underway. Hopefully we can start soon.

In this newsletter you can also read about the AHDS meeting in Rotterdam. On the next three pages you can find a comprehensive report with a lot of information about the AHDS and the Triac Trial.

If you have any questions about this newsletter, please send us an e-mail at a.aleman@erasmusmc.nl.

Neonatal screening

As explained in this newsletter one of the problems with the AHDS is its late detection.
To be able to diagnose the AHDS sooner, we are trying to accomplish a neonatal screening that includes T3 and T4.

As a first step, we will determine if the abnormal T4/T3 ratio is already present at birth. Therefore, we would like to obtain the neonatal screening cards of boys with the AHDS.

We would like to ask if the parents can request the original cards (filter paper) of the neonatal screening and send it to us. In the Netherlands this blood is stored for five years after birth. This can be different in other countries.

Please contact us at a.aleman@erasmusmc.nl if you have any questions and if you are able to send us these cards.

AHDS meeting Rotterdam

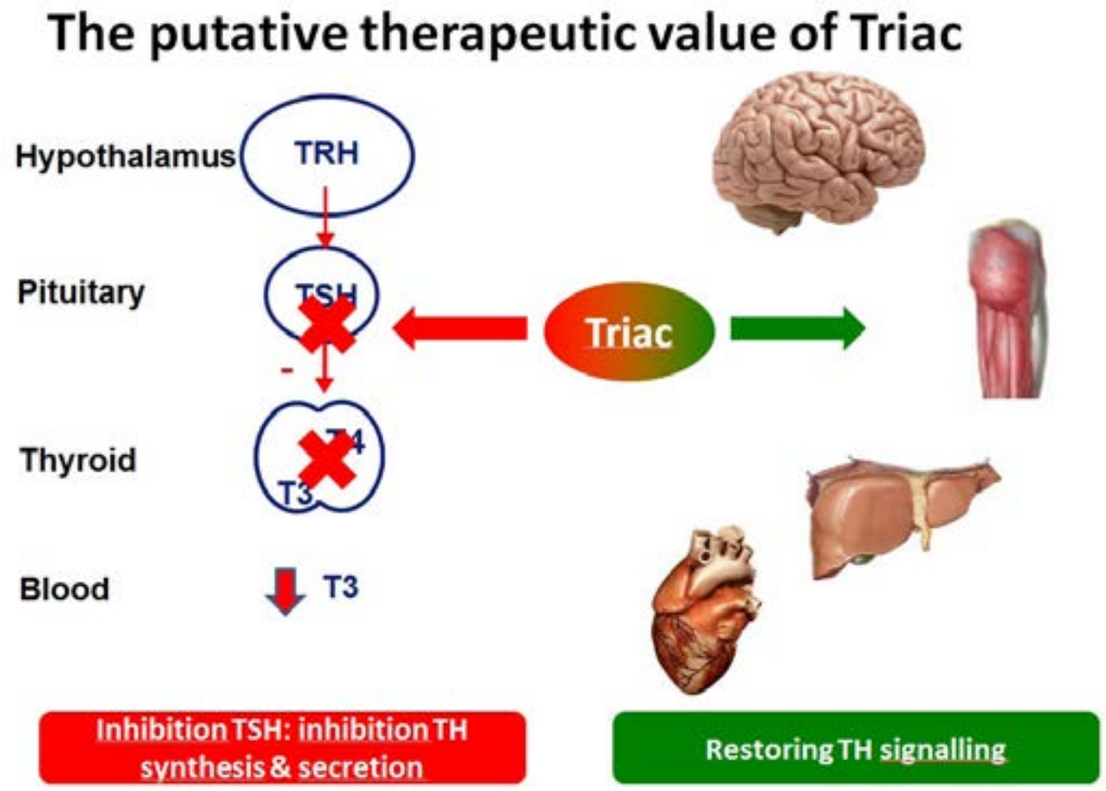
Tuesday December 8th 2015 the Allan-Herndon-Dudley-syndrome meeting took place in the Erasmus MC. Almost all Dutch parents of Triac Trial patients were present. Information was given about the AHDS and the first (preliminary) results were discussed. There was also attention for the follow-up: what happens after the Triac Trial?

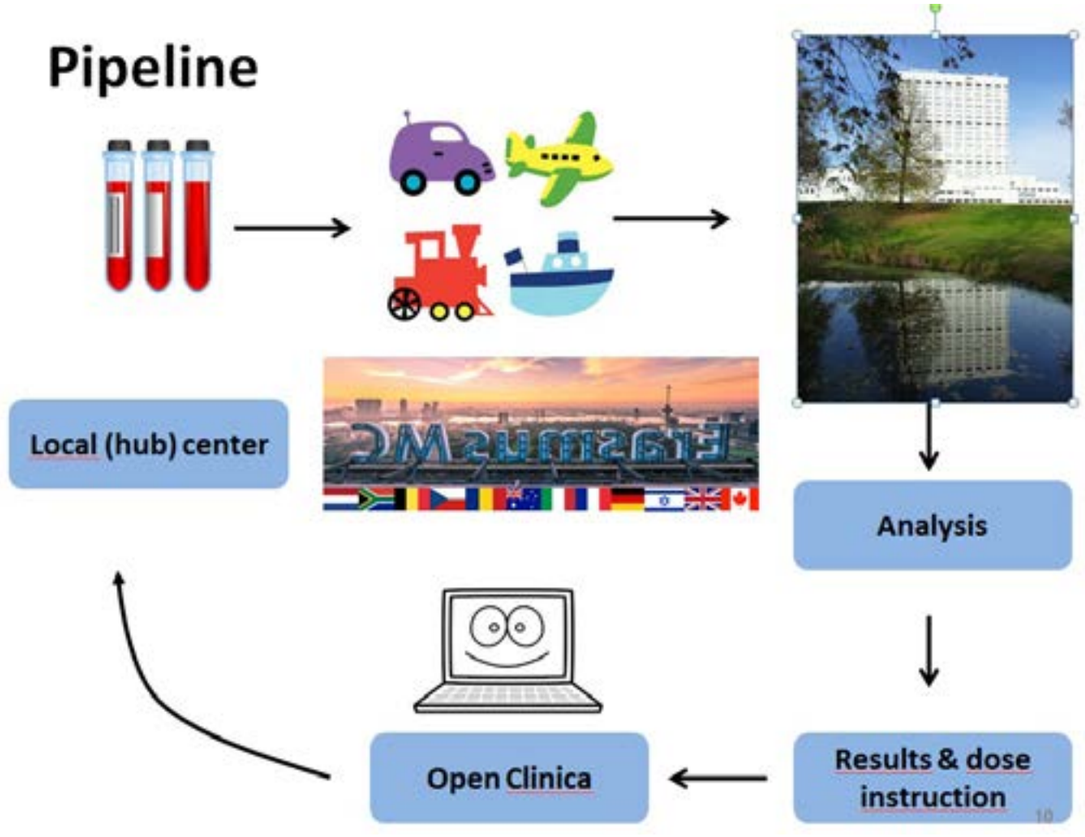
Edward Visser, principal investigator of the Triac Trial, first introduces thyroid hormones and their function, as covered in the last newsletter. Then he explains what happens if something goes wrong in this process. People with hyperthyroidism (too much thyroid hormones, T3), like people with the AHDS, present with several symptoms such as nervousness, increased heartrate, sweating, diarrhea, osteoporosis and weight loss. Besides the problem of too much T3 in the blood, there is too little T3 in the brain of AHDS patients. The reason for this is a defect in the thyroid hormone transport channel MCT8, which is needed by T3 to enter the brain. The low T3 levels in the brain cause a combination of developmental delay, dystonia (high muscle tension), and hypotonia (weak muscles). Because of this, children with the AHDS have difficulties with sitting upright, are mostly unable to walk and there is little or no speech development.

The search for an effective treatment

For an effective treatment of the AHDS, it is important to solve two problems. Firstly, thyroid hormone needs to enter the brain. Secondly, the toxic T3 levels in the blood affecting other tissues (e.g. muscle, heart) should be lowered. These symptoms should be improved by a drug that is able to replace the function of thyroid hormones in the brain and at the same time lowers the thyroid hormone level in the rest of the body. In a joint effort of different laboratories, the thyroid hormone analogue Triac was discovered to meet both requirements.

Because Triac is already a registered medicine in France, we know it's a safe drug. With the Triac Trial we investigate if Triac is an effective and safe drug in people with the AHDS.





The Triac Trial

Stefan Groeneweg, coordinator of the Triac Trial, tells more about the Triac Trial. After preclinical studies we decided to start a clinical trial in humans, where patients with the AHDS are treated with Triac: the Triac Trial. The first Dutch boys/men with the AHDS were invited at the end of 2014 for a thorough baseline visit, including clinical examinations, neurological and neuropsychological testing, testing, cardiac evaluation and blood sampling.

After all the tests, we started Triac in a low dose, which we increased carefully if necessary, until the thyroid hormones (T3) were within normal range. The participants are regularly checked by their own doctors. After one year the same tests will be performed as on the baseline visit to fully evaluate the putative effects of Triac.

During the study there are a few things we monitor. First of all the thyroid function tests. Secondly, the blood levels which reflect the amount of thyroid hormones in different organs. Thirdly, we check if there are any side effects of Triac. Lastly, we monitor the development and function of the brain.

Subsequently, we were contacted by many doctors and parents from other countries who were interested to participate in the Triac Trial. At present, we collaborate with many different doctors from all over the world, thereby establishing and expanding the global AHDS network. All patients adhere to the same research protocol. The blood samples are analyzed in the Erasmus MC, followed by feedback on dose adjustment for each individual participant.

What has happened during the treatment with Triac in patients? The interim results suggest that treatment with Triac lowers the thyroid hormones in the blood which is accompanied by favorable effects on the body. Obviously, we need more patients treated with Triac to fully evaluate the effects on the longer term.

Looking into the future

Because the AHDS is very rare and patients are spread all over the world, the knowledge about the AHDS is also scattered all over the world. Most doctors have only seen one, or a few patients with the syndrome. It is very important to bundle knowledge and expertise, allowing patients, parents and doctors to benefit from it. In this context, the Triac Trial has certainly contributed to the re-enforcement of the global AHDS network and the establishment of international collaborations. This is a pre-requisite to successfully move forward in the optimization of care and development of novel treatment strategies for patients with a rare (genetic) disorder.

One of the current challenges with the AHDS is its late detection. This is mainly due to the insufficient awareness of this disease. In addition, the thyroid hormone tests which are used to screen for thyroid disorders, TSH and free T4, are not immediately providing clues. In contrast, T3 levels are without exception elevated in AHDS patients.

To be able to diagnose the AHDS sooner, we are trying to accomplish a neonatal screening that includes T3 and T4. As a first step, we will determine if the abnormal T4/T3 ratio is already present at birth. Therefore, we would like to obtain the neonatal screening cards of boys with the AHDS.

Systemic phenotyping (the mapping of features and characteristics of the AHDS) is highly important to help doctors make a diagnosis. It also feed to guidelines on adequate monitoring and treatment of the AHDS. With help from doctors and parents from all over the world, we would like to find the answers to different questions. What was different in the development? When emerged the first problems? When were abnormalities seen in blood tests and scans? Were there problems with feeding? Was the growth normal? How was the communication development?

At the moment we are developing a questionnaire to help get information about all these things from doctors and parents. We hope you can all help us with this challenge by providing us with all the information needed.

After the Triac Trial

For most Dutch participants the Triac Trial is almost finished. An important question that arises is: how to proceed now? Until the final analysis of all patients treated worldwide has been carried out, we will continue to treat every patient with Triac.

At present, we are centralizing all care for AHDS patients in the Erasmus MC. With this we can coordinate the Triac treatment, screen for known problems that occur with the AHDS and give treatment advice for local doctors. A similar plan will be proposed for patients living outside The Netherlands.

We will continue to provide information through this newsletter and soon also through the improved mct8.info website.