Erasmus MC
University Medical Center Rotterdam

Fourth edition, November 2017

Newsletter AHDS/ MCT8 Deficiency

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

this is the fourth newsletter in our series of newsletters on the AHDS or MCT8 deficiency. In this edition, you can read about the progress of the Triac Trial, the genetic basis of the AHDS and much more.

Progress of Triac Trial

Currently, the Triac Trial is ongoing in several countries. The Dutch patients have finished the trial period, as well as a number of patients in other countries. Inclusion of new patients in the trial is stopped.

Genetic background and inheritance of AHDS

All the information that is required for the human body to function is encoded in the DNA. DNA contains thousands of genes and is found in the nucleus of each cell in the body. The DNA is stored as 2 sets of 23 chromosomes, of which 1 set is inherited from each parent. Of these 23 chromosome pairs, 22 pairs are identical between males and females, called the autosomes, whereas 1 pair (the sex chromosomes) is gender specific. Males carry 1 X-chromosome and 1 Y-chromosome (XY), whereas females carry 2 X-chromosomes (XX). This means that males have 2 copies, or alleles, of the genes located on the 22 autosomes, whereas they have only 1 copy of the genes that are located on the X- and Y-chromosome.

Each gene contains the information to make a unique protein. The SLC16A2 gene contains the information to make the MCT8 protein and is located on the X-chromosome. Thus, females carry 2 copies of the SLC16A2 gene and males only 1. The AHDS is caused by a mutation (an error), in the SLC16A2 gene. In most cases, this will result in the production of an incorrect MCT8 protein that is unable to transport thyroid hormone. Since males only have 1 copy of the SLC16A2 gene, mutations will result in the absence of functional MCT8 and, thus, AHDS.

How does a mutation in SLC16A2 occur in a child? There are two possibilities. First, the mutation occurs spontaneously during the earliest developmental phase in the fetus (see Figure 1A). Second, the mutation is inherited from the mother (see Figure 1B). A mother, who has a mutation in one of the SLC16A2 alleles, is called a female carrier. In female carriers, the healthy X-chromosome can compensate for the loss of the X-chromosome that contains the mutation and, thus, female carriers in principle do not develop AHDS. Very rarely, the compensatory mechanism in female carriers fails, resulting in the AHDS. Male offspring of a female carrier typically have a chance of 50% to inherit the SLC16A2 mutant allele and, thus, to develop the AHDS. Similarly, the female offspring have a 50% chance to be carrier of the same mutant SLC16A2 allele. Therefore, the AHDS typically affects males (see Figure 1).

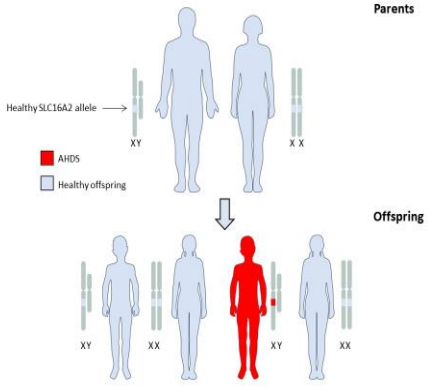


Figure 1A: Spontaneous mutation

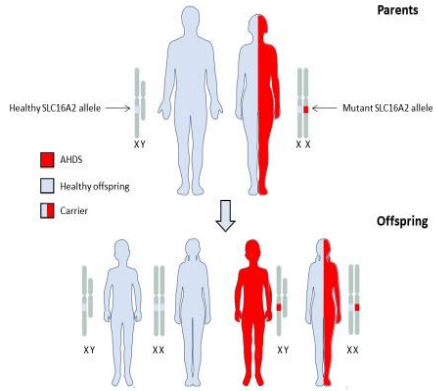


Figure 1B: Inherited mutation

Please contact your doctor for referral to a genetic counselor in case you have any questions regarding the inheritance of the AHDS or risks for future children or family members to be affected by the AHDS.

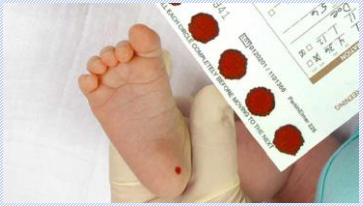
Neonatal screening

As mentioned in the third AHDS-newsletter (April, 2016), late detection is one of the problems in the care for children with MCT8 deficiency, because symptoms are not present at birth, but become apparent over time. Neonatal screening is an instrument used to diagnose (rare) genetic disorders as early in life as possible. Currently, the AHDS is not included in neonatal screening programs. To diagnose the AHDS sooner, inclusion of a diagnostic test in the neonatal screening would be advantageous.

As a first step, it is important to investigate if the abnormal thyroid function tests are already present at birth. Therefore, we would like to obtain the neonatal screening cards of boys with the AHDS.

As mentioned previously, we would like to ask if the parents would be willing to request the original card (filter paper) of the neonatal screening and send it to us. In many countries, the original filter papers are kept for a fixed period.

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



International Patient Registry

In most countries only few boys with MCT8 deficiency have been identified, often after a long diagnostic trajectory. Therefore, knowledge, experience and expertise among medical doctors about the AHDS is often limited, isolated and scattered throughout the world. International collaborations among doctors, researchers, parents and families that care for boys with the AHDS are required to share the available knowledge, experience and expertise. We believe that this is the key to improve the medical and daily care for each individual patient with the AHDS worldwide. For this reason, we have established an International Patient Registry for MCT8 deficiency in which anonymized clinical information will be aggregated. This will help to detect common signs and symptoms and clues that may facilitate an earlier diagnosis. Moreover, localization of the AHDS patients throughout the world will greatly help to bring potential new therapeutic approaches towards clinical trials and daily practice. More information about the Patient Registry will follow in the next editions of this newsletter.

Goodbye to Arjanne Aleman

Arjanne Aleman, involved in the Triac Trial as research nurse since 2015, has left the research team. We knew on beforehand that her position would be temporarily as she was very determined to use her talents and skills for people in dangerous and conflict countries. She has recently got a job in an international aid organisation. We are very grateful for all the dedicated work she did for the project! Arjanne, we wish you all the very best in your new job. Take care!