HCHWA-D information day LUMC November 9th 2019

Report by Sanne van Rijn, HCHWA-D Association

Prof. Dr. Mark van Buchem

Opening ceremonies were performed by Prof. Dr. Mark van Buchem, radiologist at the LUMC and member of the scientific advisory council of the Dutch CAA Foundation. Mark spoke of the relationship between CAA and HCHWA-D. CAA is a geriatric disorder affecting 1 out of 4 people above the age of 60: causing brain haemorrhage as a result of amyloids.

The pathology is similar to HCHWA-D, but with this difference: the onset is at a later age, and the condition is not hereditary. CAA cannot be determined while the affected person is alive, since the protein is not visible on scans; this makes research into the disease difficult. Here is a clear difference with HCHWA-D, since this can be confirmed by genetic testing. This gives HCHWA-D research global significance. Which means that not only Katwijk, but also families affected by the disorder in Australia, are now subject to closer scrutiny.

In April of 2019 researchers from the Netherlands, America and Australia, as well as the Dutch CAA Foundation and the HCHWA-D Association, came together for a day, in order to compare notes on the search for a medicine and our proposed agenda. One of the steps agreed to is that of a new cooperative of researchers from the various continents. In January 2020 Mark, together with Prof. Dr. Marieke Werner, will be visiting Australia and the families there. The HCHWA-D Association will join them there.

Prof. Dr. Steven Greenberg (handout is available: mail svanrijn@hchwa-d.nl)

Steven and Mark met several years ago, during Mark's sabbatical at Harvard. Steven, a prominent CAA researcher, noted the similarities between CAA and HCHWA-D and they decided to join forces. Since then there has been close collaboration between Leiden and Boston.

Steven expanded on CAA: its incidence, its symptoms, the present lack of effective treatment. The importance, also, both with CAA and HCHWA-D, of using blood thinners cautiously, of avoiding high blood pressure and of minimizing alcohol intake (no more than one glass a day.)

In addition, he addressed the recent news of a Alzheimer remedy about to be marketed, Aducanumab, and the question of its possible effectiveness in the treatment of CAA and HCHWA-D. In the first place, this medicine is only in an experimental phase. It does not heal the disease, though it does appear to reduce memory loss. The plaques which are associated with Alzheimer differ from the HCHWA-D proteins, and are easier to remove from the brain. Also, the medicine can have significant side effects, in that it may produce swellings in the brain.

Steven went on to describe developments specific to research on HCHWA-D, namely the potential of RNA-therapy (a collaboration between Amylon and LUMC) and the start in 2020 of the Minocycline trial (LUMC). Minocycline is an antibiotic that may possibly reduce inflammatory reaction in the brain.

These studies are part of a larger research network in the Netherlands, America and Australia, all working to find a medicine for HCHWA-D and CAA. 'Natural History Studies', studying the progression of the disease, plays a significant role in this research. For instance: the discovery, through EDAN, that the protein amyloid is present before the onset of symptoms.

Workshops

Subsequent to the plenary session there was opportunity to follow presentations in smaller groups on various subjects. The following detailed summaries cover the sessions I was able to participate in.

Prof.Dr. Marieke Werner – BATMAN

Marieke spoke of the soon to commence BATMAN (or: minocycline) study. Minocycline is an antibiotic, freely available on the market, and used for example against acne. Previous research on mice indicates that it may reduce inflammation in brain tissue resulting from amyloids and bleeding.

The study will take place next year. The plan is for the participation of 30 HCHWA-D and 30 CAA patients, who have had only microbleeds or a maximum of one haemorrhage more than three years ago. They will participate for 6 months, using the medication daily. Prior to and at the end of those 6 months neuropsychological tests will be performed (such as a memory test), as well as a lumbar puncture; the latter to see whether there has been a decrease of protein in the brain.

Participation means that a participant may possibly be included in a (placebo) control group. Marieke understands the concerns here, and the risk that people may start experimenting with the medication independently. This is understandable, but may also mean that there are too few people for the research to be valid, with the result that physicians cannot prescribe this medication in case of HCHWA-D. As long as the trial continues, one can not participate in other medical trials; after its completion one may. Participation may be combined with AURORA.

Tom Metz, MSc. - RNA therapy

Tom Metz is a PhD student with Prof.Dr. Willeke de Roon. They collaborate with Amylon and Thomas de Vlaam in the search for a way to deploy RNA-therapy against HCHWA-D. RNA is a DNA messenger. The 'wrong' gene, the mutation causing HCHWA-D, is located in the DNA. RNA is produced from within the DNA, and instructs cells to produce the APP-protein. RNA-therapy attempts to disrupt this message, preventing further production of the protein and its accumulation in the brain. The potential medication has been proven effective on stem cells (in the lab, in a petri dish) and is presently being 'tested' on mice. These mice have been 'bred' with the HCHWA-D gene and therefore develop the condition. Administering the medication to mice will demonstrate whether or not they indeed produce less proteins and develop fewer symptoms of HCHWA-D. This is one of the earliest stages of medicine testing. Further stages will need to be completed successfully in order to eventually market an effective medicine. Also here, Natural History Study is highly significant. In order to effectively deploy a (still to be discovered) medicine – that is: in the right way and at the right time – requires detailed knowledge of the course of the disease (something still lacking at this time).

Summaries of other workshops

Emma Koemans, MSc. What is Amyloid?

Emma is a HCHWA-D researcher and neurologist in training at the outpatient clinic. She gave further explanation on the APP protein and its (dys)function. It struck her that there were many questions on the progress of the disease. Why do brain haemorrhages, for example, occur only at a later age? That, she emphasized, is one of the things we do not know, since we know too little about the course of the disease, which makes studies like AURORA so important.

Sanneke van Rooden, PhD. Clinical Genetics

Sanneke is psychologist and, in addition to her research, works at the CHA outpatient clinic. Sanneke explained that everyone with questions about whether or not to do DNA tests or to participate in IVF treatments is welcome at the clinic in order to speak with a psychologist. This is also for those who are just looking for information and have not (yet) made any decisions.

Dr. Gisela Terwindt, Neurology

Gisela is Neurologist and is involved with HCHWA-D patients both as physician and researcher. It struck Gisela that she received many questions about the progress of the disease. Gisela advises making an appointment with the CHA clinic if there are specific questions, such as about the use of blood thinners, since much depends on individual factors. In addition, she recommends a healthy lifestyle – for instance in regard to stress, not smoking, moderate use of alcohol, and exercise, etc. – which is, of course, to everyone's benefit.

Dr. Huub Middelkoop, Neuropsychology

Huub is neuropsychologist and associated with among others the LUMC and Marente. He has worked with HCHWA-D patients for more than 15 years, and knows a lot about the disease. Huub emphasizes that, besides caring for your bodily health, it is also important to care for your psychological health. This applies to patients, gene carriers and potential gene carriers, but certainly also for caregivers, since these are at an extra risk of burnout.

Louise v.d. Weerd, PhD., Mouse models

Louise is particularly involved in laboratory research on HCHWA-D. This means that she is the person to speak to when it comes to cells and mice. At present, mice are used in RNA research.