Report: looking forward to a medicine, together with the scientific community – Leiden, April 10th 2019

Last April saw a special gathering in the 'Academiegebouw' in Leiden. From all corners of the world, as well as from within Leiden and other parts of the Netherlands, scientists came together to look forward. A whole day was devoted to discussion of how far along we are in research on HCHWA-D, and what is needed to arrive at our ultimate goal: a medicine for the disease. Representing the Association in order to contribute our thoughts were Jolanda Blom-de Vreugd, Jesse van Rijn, and I, Sanne van Rijn. This is my report on the day's most important conclusions.

It will not have escaped your notice that developments in the field of HCHWA-D have accelerated in recent years. This is due to a number of factors. Within the past 10 years the HCHWA-D Association and the Dutch CAA Foundation were set up, both committed to the advancement of research into the disease and stimulating study with financial contributions. In addition, the interest and commitment of researchers at the LUMC has blossomed, in company with technical advances (for instance in the areas of brain scans and DNA-techniques.) And, last but certainly not least, more and more similarities between CAA and HCHWA-D have been noted. The hereditary disease affects tens of families in the Netherlands and in Australia, but that still leaves it a rare disease. CAA, on the other hand, affects 1 out 3 older persons. This makes it a worldwide problem, comparable to Alzheimer's, but much less well known, and currently untreatable.

Finding an medication for a rare condition, with relatively few persons affected, is unfortunately (economically) not very attractive. Obviously, for a disorder occurring at the scale of CAA, it definitely is. This, for us as carriers of the gene, makes the similarity between the two a strange but happy coincidence. As a result, research into HCHWA-D accelerated in recent years, with the collaboration between (among others) Mark van Buchem (whose focus in the Netherlands is on HCHWA-D) and Steven Greenberg at Harvard (expert on CAA and active in the USA).

Every second year these partners, with financial support of the Dutch CAA Foundation, bring together in a congress researchers in the areas of CAA and HCHWA-D. At these congresses they share research results and exchange ideas for further research. The past few years have largely been concerned with increasing knowledge of the course of the disease and its progression. It will not have escaped your notice that there is still a lot to be learned in this respect. You may even have been part of one of the studies, such as EDAN or CAVIA.

These studies were aimed at research on the influence of the amyloid protein (the 'poisonous' protein that causes brain haemorrhaging when the gene mutation is present) in the brain, in blood vessels and in brain fluid, as well as a search for a so-called 'biomarker'. It is not possible, namely, simply to measure the level of the amyloid protein and to use that as a gauge of the disease's progression. Imagine that a potential medication is found, a 'drug candidate' (which you think may be effective), and you want to know whether that medication does what it is supposed to do (namely reduce the level of the protein, or at least prevent its increase). Then a manner to measure this level will be indispensable.

And so, in recent years, the search was on for an effective 'biomarker', with a number of promising results. These were shared and discussed at the September 2018 CAA congress in Lille. There the scientific advisory council of the Dutch CAA Association came together, and researchers said to each other: 'With all the knowledge we have gained in recent years and the steps we are taking, it is getting to be time to increase our focus on the possibilities of discovering a medicine.'

And so, in Leiden, a historic day took place. A day of researchers from all over the world (among others from the USA, Canada, England and Australia) discussing what is needed to commence trials on a possible medicine in the coming years. It was my honour, as ambassador of the Association, to picture for those present the impact the disease has (had) on my grandfather's family and on my own, and the suffering we may be able to prevent for future generations.

The rest of the day, with the support of two American experts in the area of medicine research for Alzheimer's, we spent on the exploration of possible routes towards a drug, and about obstacles that may be encountered. We concluded that, on the basis of Alzheimer research and the recent development of the exon skipping strategy (something Amylon, among others, is busy with), there are at least hopeful possibilities for a drug candidate.

We also concluded that with respect to the knowledge of the disease course of HCHWA-D, and of biomarkers, there is a need for continuing and more extensive research. Although the results to date are promising, the number of participants is still limited. And a rule in field research is this: the fewer participants, the less the knowledge attained. We discussed ways in which the number of participants might be increased.

It became increasingly clear to me during the meeting, among others through what Pierre Tariot of the Banner Alzheimer Center in Phoenix (USA) explained about the extent of their research programme, how important the preliminary stages of research are. Researchers didn't just happen upon an interesting drug candidate and think of a trial method to test its effectiveness. They devoted years and years to gathering knowledge on the disease and then to finding the right medicine. They created an enormous pool of participants, whom they monitored extensively. And even now, after all that trouble, it is not a foregone conclusion that the medicine they have decided on will be effective.

Foresaid preliminary work on HCHWA-D is being conducted in the shape of EDAN, CAVIA, genealogical research and AURORA. Studies like these are termed 'Natural History Studies'. And they are not only being conducted in the Netherlands. For example, in Australia, where there are hundreds of (potential) carriers of the gene, researchers at Edith Cowan University are hard at work increasing their knowledge with the help of the people there.

Yesterday we discussed the tremendous importance of combining this knowledge. Knowledge which is indispensable once you initiate a drug trial. More than that, such a trial needs approval by the relevant authorities, in order to guard patient safety. And, naturally enough, these authorities are very curious about the safety of testing a drug in a particular population. The only way you will be in a position to argue this safety is to be knowledgeable about the course of the disease and to have sufficient confidence in your 'biomarker' (the manner in which you will measure the drug's effectiveness.)

This made me scratch my head. For I often hear people say: 'I will participate in a trial only when a drug is in sight.' Once drug trials start, people will be lining up. However, such a trial will not be able to commence, if there is insufficient preliminary knowledge. And this knowledge is impossible to attain if too few people are willing to participate in the studies which are aimed at this goal.

At the end of the day we came to our conclusions and together agreed on a plan for the coming period:

- Consider how knowledge of the disease course of HCHWA-D and of biomarkers may be more widely shared, among others by augmenting the reach of AURORA

- Expanding the collaboration between Dutch and Australian researchers and contact between Dutch and Australian families
- Developing a plan to create more awareness among affected people in Katwijk of the importance of increasing knowledge and working towards a first trial
- Maintain close contact with companies that might be able to produce a medicine
- Looking for funding, because man, medicine research is so expensive!

We concluded the day with a toast and in good cheer. Yes, we have a long way to go. But we're headed in the right direction!