A very special visit to Perth, Australia

The HCHWA-D Association was founded in 2007 by my parents, Janny de Vreugd and her husband Koos van Rijn. It all started with a notice in the local newspaper and a first get-together. About 40 people were there, and it was clear that for those with the condition in the family there was need of a place to come together. A number of enthusiasts stepped up, forming the board of the Association.

The Association's initial focus was the provision of support and information. Due to the taboo surrounding the disease, a number of misunderstandings had arisen. For example: that it skips generations, or that it is more serious when inherited from one's father. For this reason, most energy was spent on open house and thematic evenings, creating an effective website, making folders and flyers and our "Zorgloket" (a access point for questions, by phone, email, or – if needed – face to face.)

Our subsequent aim was to build a network. We invested in relations with family physicians, rehab centres, care facilities and doctors at the LUMC. An important goal here was the improvement of care for people with HCHWA-D; for example, for those who suffered brain haemorrhage and were being treated as if this were a 'normal' bleed and not part of a progressive genetic condition. And also for those who were otherwise impacted: family members, those bearing genetic risk, or anyone with related questions and needs. We built close ties with the CHA-outpatient clinic at the LUMC, for example, and more recently with a newly formed "Expertise Team", part of one of the largest health care parties in the region.

Beyond that, we promoted research on the disease, for this had come to a complete halt. After professor Luyendijk and doctor Timmers' involvement during the 1980's and the discovery of the disease's genetic background in the 1990's, attention had waned. The thought that the condition might be a model for the development of Alzheimer's proved mistaken, and as a result, unfortunately, we were no longer as interesting.

But that changed, a few years ago, when professor van Buchem and professor Greenberg mutually concluded that HCHWA-D and CAA were very similar. Which meant that HCHWA-D might well a key to the solution of a worldwide problem. CAA, which affects 1 out of 4 older persons, 'the biggest disease you never heard of' as the Dutch CAA Foundation so aptly describes it.

Meanwhile, not long after the launch of the Association and its website, a certain Anna Palmer from Australia approached Janny. She told us about 'the Plug thing'. Her grandfather Jan Plug emigrated from IJmuiden to Albany in 1950 and took the disease with him. Jan had many descendants, all of whom at risk of (or in fact) suffering from HCHWA-D. As, for instance, Anna herself. Anna and Janny remained in contact over the years, and in 2018 she and her husband Rob came to visit us in Katwijk. Janny, my sister Frouke and I welcomed her and we spoke about the condition and its impact over lunch at the beach.

Around this time it began to dawn on me that we should take more notice of that Plug family at the other end of the world. In September of 2018 I was at the Lille international CAA congress, together with fellow board member Jesse. For the first time also the Australian professors Ralph Martins and Hamid Sohrabi attended the congress. They informed us of the DIAN (Dominantly Inherited Alzheimer Network) study. As part of that study they follow people for years, somewhat like EDAN, but then seeing these people once a year. Also the Plug family participates in this study.

At the congress it was decided that it was time to cooperate more specifically with the purpose of developing a medicine. Thus an international gathering was organized in April of 2019 (a meeting which was initially to take place in Iceland, then in Boston, and finally… yes, in Leiden. Not a problem, who wants to go to Iceland or Boston anyway?) Our Association was represented by Jesse, Jolanda, and myself. I was given the opportunity to speak first and to set the tone, illustrating by means of our family tree what the impact of the disease has been on us, and how many people could potentially have been 'saved' in this one branch alone. The rest of the time we discussed concrete steps which might be taken.

Also on this occasion, Ralph and Hamid were present. The evening before we had dined together, and I had spoke to Ralph extensively about the work of our Association. Once again, as at Lille, he proved to be very interested. Something like this was definitely needed in Australia.

And the thought kept recurring: how would we be able to facilitate this? Then, last November, during an information day at the LUMC, I was sitting in the lecture room while Mark did the preliminaries. He said: 'There are families with HCHWA-D in Australia as well and Marieke (professor Werner) and I will visit them in January.' PING! I looked at Jolanda, and she understood what I was thinking. During the break, we walked downstairs to greet Steven (Prof. Greenberg, also present at this meeting) and Mark. 'So,' I said to Mark, 'so you're going to Australia?' He looked at me. 'Yes, are you coming along? Why didn't we think of this earlier..' Of course we're coming along!

From January 26th to February 1st the research team met with family members. I flew a bit earlier and stayed a few days with Rob and Anna in Albany. We spoke a lot, about all sorts of things, but particularly about the condition. On one of my evenings there she invited her sisters and brother, with hangers-on and children, to come over 'in my honour'. A really special evening.

I learned a lot about them and their experience of the condition. They call it 'the Plug thing' or 'the Plug disease', since they know no others whom it affects. They are part of the DIAN study, but receive little information. Medical practitioners here know little to nothing about the disease. So there were a great many questions. Also about the origin of the condition, which caused me to work out their family tree. This triggered a thought: by reason of medical ethics the Leiden University Medical Center cannot do that, but we of course are perfectly capable of doing it ourselves! All the information is readily available online. It is a bit of work, but this does allow us together to discover more about our common ancestors *and* the number of people impacted by HCHWA-D . And that is so very important!

After that it was time to meet Mark, Marieke and Jolanda in Perth. The first evening we went for drinks in the hotel bar and I brought them up to date on my experiences so far. 'It's as if they are where we were 10 years ago. In coming to terms with the condition, the information which they can access, and their hopes for the future,' I told them. It was helpful to start the week with this information. Clarifying.

The next evening Jolanda and I dined with Dini Plug, with whom Ralph had brought us into contact. She is 50, her father died from the condition, and she has 11 brothers and sisters. Some time ago, during her studies at Edith Cowan University, where Ralph and his team work, she heard him speak on the radio about early onset Alzheimer's and the APP protein. That triggered her, and she emailed Ralph about the 'Plug thing'. Ralph's initial reaction was that this must be a joke: for how could they not be aware of this family and the condition within it? But after meeting face to face it became clear that this family had to be included in DIAN, though a number of obstacles needed to be overcome to make this possible. Dini became the liaison with the family and maintained contact with Ralph and his team. When there was information to share with interested family members, she passed it on.

We spoke with her about how they had discovered that *this* was the family condition, how they dealt with it, what participation in DIAN means to them and how it may or may not benefit them and about the future. Once again a special encounter, one that left a deep impression on both Jolanda and myself.

The next evening was one that I had looked forward to with great anticipation. Armed with stroopwafels and drop we met as many as 50 family members in a well-filled lecture hall. Attendance was beyond our expectations, not in the least because there were so many younger people present. In half an hour I told them about the beginnings of the Association, about what we do, about our collaboration with (among others) Marieke and Mark, and about the Dutch CAA Foundation and the Kattukse Brainweek. With the aid of photos I led them through 13 years of the HCHWA-D Association's history. A very special retrospective, also to ourselves, on a turbulent period.

After me came Mark, who told them of his personal journey with HCHWA-D. He spoke of encounters which changed his life: with Steven, discovering the condition's likeness to CAA, with my mother and me, our hopes for the future which we placed in them and the lifelong commitment he and Jan Fens subsequently made, the establishment together of the Dutch CAA Foundation, and last of all the connection with Hamid and the realisation that the research being carried out at opposite sides of the globe could and should be combined. Mark said that this evening's presentation was one of his most significant life moments and that he sensed its historical nature.

Finally there was Marieke, who spoke of research projects to date (EDAN, CAVIA and the genealogical research) and their results, and of the future with AURORA and BATMAN. She too emphasized how special to her the evening was, she spoke of her personal involvement and her hopes for the future. And about the importance of Natural History Studies (studies on the progress of the disease) for finding a possible medicine.

There was a lot to discuss afterwards. People finally felt heard and seen. They had had no idea of how many fellow-sufferers there were in the Netherlands, or of how much progress has been made in recent years. There were questions about how DIAN relates to research in the Netherlands, what recommendations physicians in the Netherlands were offering patients or potential carriers, and of course what is involved in setting up an Association like ours.

We explained to them the benefits of sharing things with each other and promoting common interests, and how influential an Association can be in steering research and care. What it's like to start 'from scratch' and to watch how things grow. Sometimes – often – in directions we could never have foreseen. That very evening Dini and a number of others decided to establish an Australian branch of the Association. What a great idea that was! And in the following days we did what we could to assist them in this.

The next day we really needed time to process all our experiences. There was so much to deal with! So many stories, encounters and initiatives. Very special to have been able be part of. But there wasn't that much time, for in the evening a dinner had been planned with a number of family members. With them the discussion continued: about what their impressions were, how we deal with the condition in our respective families, and what they might contribute here in that respect.

Thankfully, Jolanda's and my schedule from that point on was not very demanding, and we had opportunity to focus on contact with the Australian branch and their plans for its establishment, while Mark and Marieke kept busy getting acquainted with the research team here and further setting out the common research agenda. For in the end, DIAN and AURORA will have to be brought together, and the data gathered shared – both to the greatest possible extent. In addition they made

acquaintance with a neurologist and, influenced in part by their encounters with family members, impressed upon him the importance of specialised care. Not that everything was in place after this meeting, but it seems likely that the next few weeks will see progress on this score. A hopeful development for family members here, in any case.

Beside these very special developments in our collaboration with the Aussies, this week also provided an opportunity to Jolanda and myself, as representatives of the Association, to further reinforce our connection with Mark and Marieke. Once again we realize how very special this collaboration is and how it has continued to develop. On our last evening together we looked back and discussed future steps. We all feel that we have arrived at a crucial stage. Things are really happening. And it is important to keep talking with each other, to keep seeing each other, and to keep informing each other. All of us are going to make a real effort here.

This morning Jolanda and I looked back on this week, incredibly thankful to have done and experienced this. Feeling that we have really made a difference, that we have been witness to something of which – years from now – we will look back and say: 'We were there!' With many new friends and even in some way a new family, for from now on we are mutually connected. With a new motto: United We Stand!