

# A prospective view on disease course and associated biomarkers in Hereditary Cerebral Hemorrhage With Amyloidosis Dutch type (HCHWA-D)

Published: 16-02-2018

Last updated: 12-04-2024

To follow up presymptomatic and symptomatic profiles including (early) disease stages and (early) biomarkers of disease progression and to elucidate pathophysiological mechanisms, we will investigate HCHWA-D patients at different ages (both...

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruiting
<b>Health condition type</b>	Central nervous system vascular disorders
<b>Study type</b>	Observational invasive

## Summary

### ID

NL-OMON55383

### Source

ToetsingOnline

### Brief title

HCHWA-D follow-up study

### Condition

- Central nervous system vascular disorders

### Synonym

HCHWA-D, hereditary cerebral amyloid angiopathy, Hereditary Cerebral Hemorrhage With Amyloidosis Dutch type

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum

**Source(s) of monetary or material Support:** Brain@Risk, Alnylam, Biogen, Hartstichting: Dekkerbeurs

## Intervention

**Keyword:** biomarkers, cerebral amyloid angiopathy, disease course, hereditary

## Outcome measures

### Primary outcome

- Long-term disease course in HCHWA-D

Long-term disease course will be determined by the occurrence of presumably HCHWA-D related symptoms; by cognitive performance (Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB); Montreal Cognitive Assessment (MoCa); Trail Making Test (TMT)), by use of the modified Rankin Scale (mRS), the National Institutes of Health Stroke Scale (NIHSS) and Barthell Index (BI). Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression Scale (CES-D), Neuropsychiatric Inventory Questionnaire (NPI-Q), Starkstein Apathy Scale and Prikkelbaarheids schaal (PS) questionnaires will be used for screening for depression, anxiety and psychopathology. Furthermore Headache/Migraine questionnaires will be performed. In the TRACK D-CAA subgroup only the following additional neuropsychological tests will be assessed annually: Controlled Oral Word Association Test (COWAT letters F-A-S), Boston Naming Test (BNT, 30-items), Cogstate computerized battery and Clinical Dementia Rating scale (short version; CDR-s). The following questionnaires will also be assessed annually: the International Physical Activity Questionnaire short form (IPAQ-SF),

(IQCODE) and the Frenchay Activities Index (FAI).

- Prevalence of biomarkers in CSF

Concentrations of A $\beta$ 40, A $\beta$ 42, t-tau, and p-tau181 in CSF.

- Prevalence of MRI markers

The presence of microbleeds, microinfarcts, white matter hyperintensity, large perivascular spaces, striped cortex, cortical subarachnoid haemorrhage and/or superficial siderosis on 3 T and 7T MRI

White matter tissue integrity will be assessed with quantitative MR measurements.

Presence of beta-amyloid deposition derived from [18F]Florbetaben PET-CT with SUVR and centiloids as indicators of amyloid load in the TRACK D-CAA subgroup.

## **Secondary outcome**

- Other study parameters

Other parameters of this study will include date of birth, gender, current medical conditions, in women also information on female medical history such as number of pregnancies, menstruation cycle and menopause will be retrieved), daily intake alcohol/drugs/cafeine, smoking, medication, cardiovascular risk factors, neurologic history (including previous ischemic or hemorrhagic stroke), BMI, blood pressure and APOE genotype and, unless already known, the presence of the single base mutation at codon 693 of the amyloid precursor protein gene on chromosome 21. Blood samples will be analyzed for routine

laboratory tests such as glucose, cholesterol spectrum, thrombocytes, APTT and PT). CSF samples will be analyzed for routine clinical parameters (cell count, protein, glucose).

## Study description

### Background summary

Intracerebral hemorrhage, sporadic cerebral amyloid angiopathy and HCHWA-D Intracerebral hemorrhage (ICH) is a frequent subtype of stroke but the research in this field has received far less attention than ischemic stroke. Until now, only sparse information is available on the different causes of ICH and the factors that influence the onset of ICH, recurrence rate and outcome. Unlike most other stroke types, the incidence, morbidity and mortality of ICH have not declined over time.(3,4) Of the primary ICH, one third is associated with cerebral amyloid angiopathy (CAA). CAA is characterized by the deposition of amyloid- $\beta$  (A $\beta$ ) peptide and degenerative changes in the capillaries, arterioles, and small and medium sized arteries of the cerebral cortex, leptomeninges, and cerebellum. Most cases of CAA are considered to be sporadic but worldwide there are also a few familial forms of CAA. In general, hereditary forms of CAA have an earlier onset and more severe clinical manifestations than sporadic cerebral amyloid angiopathy (sCAA). Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) is an autosomal dominant Dutch form of CAA, in which the amyloid angiopathy is pathologically and biochemically similar to sCAA. The disease is characterized by (repeated) intracerebral hemorrhage and dementia. A $\beta$  is generated by sequential cleavage of amyloid precursor protein (APP) by alpha-,  $\beta$ - and  $\gamma$ -secretases. In the early nineties a point mutation in codon 693 of the gene encoding the APP was found in HCHWA-D, resulting in a Glu-->Gln amino acid substitution at position 22 of the A $\beta$ -protein region on chromosome 21 influencing correct cleavage.(5) HCHWA-D is considered to be a monogenic model for sporadic cerebral amyloid angiopathy and a unique opportunity to study the influence of vascular amyloid on ICH.

### Cerebral amyloid angiopathy and MRI and CSF biomarkers

Cerebral amyloid angiopathy is associated with a high prevalence of imaging markers of small vessel disease, including lobar cerebral microbleeds (CMB\*s), white matter hyperintensity (WMH), large perivascular spaces (PVS), cortical subarachnoid haemorrhage (cSAH) and superficial siderosis (SS). The Leiden HCHWA-D research group recently published new data on biomarkers in HCHWA-D. In a 7T MRI study it was shown that microinfarcts are one of the earliest markers of the disease, seen in 30% of presymptomatic patients.(6) Moreover a new cortical pattern was discovered, namely a striped cortex.(7) Furthermore

vascular reactivity measured by changes in blood-oxygen-level-dependent (BOLD) signal after visual stimulation was decreased in HCHWA-D (8). In addition, a recent study showed both CSF A $\beta$ 40 and A $\beta$ 42 concentrations are markers of the earliest phase of HCHWA-D related pathology before clinical or radiological findings appear. (9)

In HCHWA-D patients, tissue changes that appear normal on conventional MRI (the so-called normal appearing white matter (NAWM)) have not been investigated, so far. Histopathologic studies of NAWM of non-genetic forms of small vessel disease (SVD) have shown tissue changes consisting of lower myelin density, activated endothelium and a looser axonal network (Gouw et al, JNNP 2011). These MRI \*invisible\* changes may also occur in HCHWA-D patients and may be of clinical relevance; using quantitative MR measurements (e.g magnetization transfer imaging, relaxation time measurements) these changes can be characterized in vivo.

#### Biomarkers, clinical symptoms and disease progression

Symptoms of HCHWA-D include (often recurrent) ICH and dementia occurring at a relatively young age. The mean age of the first ICH is 50 years. (10) Other clinical symptoms of CAA include headaches, migraines, and epilepsy. Previous studies have shown that approximately 10% of ICH patients suffer from at least one seizure after their ICH.(11) The prevalence of epilepsy in HCHWA-D is unknown. One study suggested that epilepsy was only present in symptomatic HCHWA-D mutation carriers with at least one ICH.(12) However, epileptic seizures in a presymptomatic mutation carrier have also been seen in our clinic (unpublished). Patients with a cortical (lobar) location of the hemorrhage are especially prone to late seizures (occurring >7 days after stroke), (10) as lobar microbleeds are often found in CAA, this finding suggests a link between late seizures and cerebral amyloid angiopathy.

Migraine was suggested as an early symptom of HCHWA-D. (12) Headaches and migraines in HCHWA-D patients usually start several months to years prior to the first haemorrhage.(13) It is uncertain whether the reported migraines are \*true migraines\* or caused by amyloid spells. These amyloid spells are described as brief transient neurological episodes with symptoms which show similarities to a migraine aura.(14)

The prevalence for seizures, headaches, migraines and other clinical symptoms in HCHWA-D has never been studied in a truly and long lasting prospective design. Little is known about the relation between MRI/CSF/blood biomarkers and the clinical symptoms and signs such as future hemorrhages. A cross-sectional study reported that the volume of white matter hyperintensities seemed to have the closest association with cognition, and microbleeds the closest association with symptomatic intracerebral haemorrhage.(15) Furthermore, recent data show a correlation between MRI markers (high microbleeds count and white matter hyperintensity volume) and CSF biomarkers (decreasing A $\beta$ 40 concentrations) in HCHWA-D mutation carriers.(9) Longitudinal studies in this unique hereditary CAA group are required to search for and provide support for associations between clinical symptoms and (bio)markers and to provide biomarkers to predict clinical outcome and treatment efficacy.

Treatment for CAA, and HCHWA-D as model for sporadic CAA

Unfortunately, currently no evidence-based treatment options are available for CAA. With the lack of therapeutic options, clinicians are restricted to hypertension management and avoiding antithrombotic and anticoagulant therapy to prevent worsening of secondary injury as much as possible.

Recently, the idea was formed that HCHWA-D, as the hereditary form of CAA, could serve as a model for sCAA based on a similar pathological and biological basis between the two conditions. As subjects with the genetic mutation can be identified before the onset of clinical symptoms the efficacy of disease modifying treatments can be investigated in the earliest stage of the disease, even before symptomatology, and the detrimental effects of amyloid deposition in the neurovascular system could be attenuated and possibly even stopped. Furthermore, these investigations could elucidate possible treatment effects for the much more widely prevalent sporadic form of CAA.

In order to push the development of therapeutic strategies forward, a prospective follow-up study with short follow-up times in a HCHWA-D cohort seems essential. With repeated imaging, CSF and potential blood biomarkers, the associations between clinical symptoms and disease biomarkers can be established. These tools are crucial for the development of a treatment trial in CAA. Therefore, in a subgroup of presymptomatic and early stage subjects (the TRACK D-CAA subgroup) annual assessments will be performed to show how specific markers change in the early phase of the disease, against which a future treated cohort of patients can be contrasted to show the efficacy of new treatments.

## **Study objective**

To follow up presymptomatic and symptomatic profiles including (early) disease stages and (early) biomarkers of disease progression and to elucidate pathophysiological mechanisms, we will investigate HCHWA-D patients at different ages (both symptomatic and presymptomatic), and (where necessary) compare them with healthy control subjects. We aim to identify characteristics and mechanisms specific to HCHWA-D, using a unique collection of different techniques/ methods. We will:

1. Perform an extensive clinical work-up using structured interviews and physical examination during regular intervals to investigate long-term disease course in HCHWA-D
2. Investigate hallmarks of amyloid function in CSF, to identify course of amyloid and related biomarkers with disease progression
3. Investigate markers of MR- and PET-imaging and their evolution over time with disease progression
4. Store blood and CSF of HCHWA-D patient for biobanking purposes and future research

## **Study design**

Our study design is a prospective cohort study. A subgroup of 50 participants will be followed more intensively (TRACK D-CAA subgroup).

## **Study burden and risks**

To learn more about the pathophysiology, progression and prognosis of HCHWA-D we need to investigate HCHWA-D patients. The mutation carriers may benefit from more insight into their disease. By investigating factors like clinical symptoms, outcome and disease markers in prospective design we hopefully will learn more about disease course and about the relation between MRI markers, biomarkers in CSF, clinical symptoms and disease progression. A recent publication emphasizes that both CSF A $\beta$ 40 and A $\beta$ 42 concentrations are markers of the earliest phase of HCHWA-D related pathology, before clinical or radiological findings appear. (9) It is important to identify course of amyloid and related biomarkers with disease progression for future therapeutic studies.

Moreover this study could eventually lead to much more insights about both sCAA and ICH in general. Patients will be informed extensively about the potential risks of the study procedures, after which written informed consent will be obtained.

Blood withdrawal via venous puncture in the elbow has a very low rate of adverse events. The needle puncture may cause bruising and in very rare cases an infection of the skin or blood vessel may occur at the puncture site.

The risks of MRI are minimal (risk of everyday life), because there are no consequences to the health of the participant. Potential risks from the MRI study include movement of ferromagnetic objects in the body. Furthermore, some subjects may feel claustrophobic in the restricted space of the MR scanner. The most frequently occurring complication of lumbar puncture is post-punctional headache. This may occur in 25% of patients when standard lumbar puncture needles are being used and much rarer (12%) when atraumatic spinal needles are used. If post-lumbar puncture headache occurs, subjects should take bed rest, drink ample water, and may use paracetamol if required. If the post-lumbar puncture headache persists for more than a week, a blood patch may be considered which is usually effective in treating the headache. Very rarely, infection such as meningitis or spinal abscess may occur.

The radiation risk of [18F]Florbetaben is similar to other radiopharmaceuticals and contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. This risk is however relatively low and in our opinion outweighs the (scientific) benefits of this study.

Also, the radiation expose for the [18F]Florbetaben PET-CT is within the limits provided by the Nederlandse Commissie voor Stralingsdosimetrie for categorie IIb research (see Appendix B for details and paragraph 6.4 of this research protocol). The range of 1 to 10 mSv per year corresponds to a maximum risk of five in ten thousand. To place this level into context, this range corresponds to the same order of magnitude as the annual natural background radiation (per

year) in various parts of the world.

## Contacts

### Public

Leids Universitair Medisch Centrum

Albinusdreef 2  
Leiden 2300 RC  
NL

### Scientific

Leids Universitair Medisch Centrum

Albinusdreef 2  
Leiden 2300 RC  
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

1. Age  $\geq 18$ y
2. Presence of either the APP mutation or an (earlier occurrence of) ICH on CT/MRI suspect for CAA and a family history (first degree relative) of HCHWA-D.
3. Ability and willingness to provide written informed consent

Additional criteria for TRACK D-CAA subgroup:

1. Age 25-60 (inclusive) years old
2. Presence of APP mutation at position 693 (100% carrier) or one first-degree relative with the mutation (50% carrier in case participants do not want to



know their mutation status)

3. No symptomatic ICH or maximum of 1 symptomatic ICH > 1 year before study entry with ADL independence after the hemorrhage.

## Exclusion criteria

1. Contra-indications for 3T/7T MRI as determined by the 7Tesla safety committee. (exclusion for a subpart of the study)
2. Contraindications for lumbar puncture (exclusion for a subpart of the study)
3. Contraindications for [18F]Florbetaben PET-CT (TRACK D-CAA subgroup only)

## Study design

### Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

**Primary purpose:** Basic science

### Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	07-05-2018
Enrollment:	150
Type:	Actual

## Ethics review

Approved WMO	
Date:	16-02-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO  
Date: 13-03-2020  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 07-08-2020  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 12-03-2021  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 17-05-2021  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 14-06-2021  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 02-09-2021  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

Approved WMO  
Date: 31-12-2021  
Application type: Amendment  
Review commission: METC Leiden-Den Haag-Delft (Leiden)  
metc-ldd@lumc.nl

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

Register	ID
CCMO	NL62670.058.17