

# Follow-up study of amyloid detection in HCHWA-D patients, a monogenetic variant of cerebral amyloid angiopathy

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The general aim of this study is to investigate if the early markers seen in presymptomatic patients predict progression of the disease. Furthermore, we can study if the disease markers we found in the mutation carriers predict disease severity.

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Neurological disorders congenital
<b>Study type</b>	Observational invasive

## Summary

### ID

NL-OMON45250

### Source

ToetsingOnline

### Brief title

Follow-up of amyloid in HCHWA-D

### Condition

- Neurological disorders congenital

### Synonym

Hereditary Cerebral Hemorrhage With Amyloidosis-Dutch type, Katwijk disease

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum

**Source(s) of monetary or material Support:** CAA foundation

## Intervention

**Keyword:** amyloid, Cerebral Amyloid Angiopathy (CAA), Hereditary Cerebral Hemorrhage with Amyloidosis- Dutch type (HCHWA-D)

## Outcome measures

### Primary outcome

1) 7T: The quantitative measure of phase shifts, visual score of cortical microinfarcts and striped cortex 2) 3T: WMH and DPVS volume and measurement of vascular reactivity, 3) CSF concentrations of A $\beta$ 40 and A $\beta$ 42, 4) Estimation of clinical severity and disease progression of HCHWA-D by using neurological and neuropsychological standardized tests.

### Secondary outcome

na

## Study description

### Background summary

Sporadic cerebral amyloid angiopathy (sCAA) is a common cerebrovascular disease of the elderly that is caused by deposition of vascular amyloid\*. The absence of reliable, non-invasive diagnostic tests is a major problem in diagnosing CAA and until now the diagnosis can only be made post mortem. A group of CAA patients with a pure form of vascular amyloid in whom a genetic basis for the disease has been identified are patients with hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D). HCHWA-D is considered to be a good model to study sCAA. In HCHWA-D patients, the presence of the disease can be determined based on a genetic test. Consequently, HCHWA-D is an ideal model to study early phases of CAA, since the presence of the disease can be assessed reliably, irrespective of the presence of signs and symptoms.

In our previous study on HCHWA-D our goal was to find early markers for sCAA based on HCHWA-D. Therefore, we used 7T and 3T MRI, cerebral spinal fluid (CSF) and clinical characteristics, such as cognitive tests, neurological measures and blood measurements. Using these methods we were able to demonstrate several early markers of the disease. 7T MRI showed that cortical microinfarcts and an increased cortical phase shift in the occipital lobe are

early markers of the disease. 3T MRI demonstrated that white matter hyperintensity (WMH) and dilated perivascular spaces (DPVS) volume are already significantly increased in the presymptomatic stage of the disease and the blood oxygen levels-dependent (BOLD) signal after a visual checkerboard stimulus was significantly decreased in the occipital lobe in presymptomatic mutation carriers. CSF analysis of amyloid- $\beta$ 40 (A $\beta$ 40) and amyloid- $\beta$ 42 (A $\beta$ 42) proteins demonstrated decreased levels in the presymptomatic stage of the disease. But also our research in the symptomatic patients showed several new markers and insights in the disease. Now, we are very interested if these (early) markers are predictive for the clinical stages of the disease and if the markers we found can predict severity of the disease.

## **Study objective**

The general aim of this study is to investigate if the early markers seen in presymptomatic patients predict progression of the disease. Furthermore, we can study if the disease markers we found in the mutation carriers predict disease severity.

## **Study design**

Combined longitudinal and cross-sectional study.

## **Study burden and risks**

This is a non-therapeutic group relatedness study. In order to achieve the aim of the study HCHWA-D patients who participated in the previous study are needed, because of the extensive presence of pure vascular amyloid and a genetically proven diagnosis and the early markers we found in these patients. To learn more about the pathophysiology and the development of CAA during the presymptomatic phase of HCHWA-D we need both presymptomatic and symptomatic HCHWA-D mutation carriers. The study day consists of two MRI scans, a neuropsychological assessment and a neurological exam which all have no consequences for the health of the participants. Lumbar puncture is optional. Contra-indications will be carefully investigated per subject to minimize the risks. Burden will be kept at a minimum by using short protocols.

## **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**

Participant in the previous study.:- HCHWA-D mutation carriers

\* Ability and willingness to provide written informed consent (see appendix).

\* Age \*18 years old.:- Control subjects

\* Age \*18 years old.

### **Exclusion criteria**

- Other definite cause of hemorrhage. Exclusion causes are excessive anticoagulation (INR >3.0), antecedent head trauma or ischemic stroke, CNS tumor, vascular malformation, vasculitis, and blood dyscrasia. - Contra-indication to MRI scanning: \* Claustrophobia \* Pacemakers and defibrillators \* Nerve stimulators \* Intracranial clips \* Intraorbital or intraocular metallic fragments \* Cochlear implants \* Ferromagnetic implants \* Hydrocephalus pump \* Intra-utrine device \* An iron wire behind the teeth \* Permanent make-up \* Tattoos above the shoulders - Specific contraindications to fMRI \* History of ischemic stroke, transient ischemic attack, carotid/intracranial artery stenosis. \* Seizure within prior year. \* Noncorrectable visual impairment. - Severe physical restrictions (completely wheelchair dependent) - Contraindications for a lumbar puncture, including any tumour, compressio medullae, signs and symptoms of increased intracranial pressure, local infections of the skin, and a coagulopathy including use of anti-coagulant drugs or platelet-inhibitors.

## Study design

### Design

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

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	20-04-2017
Enrollment:	57
Type:	Actual

## Ethics review

Approved WMO	
Date:	15-03-2017
Application type:	First submission
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	NL59968.058.17