Cerebrovascular manifestations of vascular Amyloid deposition in HCHWA-D | An assessment of the cerebrovascular reactivity in Hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D) patients using Magnetic Resonance Imaging and transcranial Doppler.

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The primary objective for this study is to evaluate the cerebrovascular reactivity of HCHWA-D patients:1. To compare the (autoregulatory) function of small brain vessels in HCHWA-D patients with matched controls using the cerebrovascular reactivity...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON44090

Source
ToetsingOnline

Brief title
Cerebrovascular reactivity in HCHWA-D

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Vascular haemorrhagic disorders

Synonym
Dutch type (HCHWA-D), Hereditary cerebral hemorrhage with amyloidosis, Hereditary Cerebrale Amyloïd Angiopathie (hCAA)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW - MEMORABEL - CAVIA

Intervention

Keyword: Cerebrovascular reactivity, Dutch type (HCHWA-D), Hereditary cerebral hemorrhage with amyloidosis, MRI, Transcranial Doppler (TCD)

Outcome measures

Primary outcome

The first set of main study parameters are related to the cerebrovascular

reactivity (CVR) measurements with MRI (without using contrast agents) and

consist of:

* cerebrovascular reactivity to visual stimuli:

Cerebrovascular blood flow change

* cerebrovascular CO2 reactivity:

Cerebrovascular blood flow change / mmHg CO2 change

Oxygenation signal change / mmHg CO2 change

The second set main study parameters are related to the dynamic cerebrovascular

autoregulation (CA) and cerebral vasomotor reactivity (CVMR) measurements and

consist of:

* Hemodynamic parameters measured by finger plethysmography with a finger cuff:

Blood pressure

Heart rate

Stroke volume

Cardiac output

Systemic vascular resistance

* Cerebral parameters measured by means of transcranial Doppler

Cerebral blood flow velocity (CBFv)

* Respiratory parameters measured through a nasal cannula using a capnograph

End-tidal CO2

Secondary outcome

The other study parameters collected during this study are related to the clinical characteristics of the study populations: date of birth, gender, arterial oxygen saturation, presence of other comorbidities, current/past medication use, daily intake of alcohol/drugs/caffeine, smoking status, body weight and neurologic history. These data will be collected through questionnaires as screening and, if necessary and the subject gives permission, through the patient*s health records at the hospital, and will also be administered on the day of scanning.

Furthermore, subjects will undergo a neurological and physical examination and take neurological and cognitive tests to evaluate cognitive functioning, speed of processing, mental flexibility, executive functioning, aphasia, memory, anxiety and depression.

Anatomical MRI-scans will be used for the post-processing of the images.

Standard laboratory blood tests will provide the measurement of hemoglobin,

hematocrit, HbA1C, plasma creatinine, glucose, cholesterol (total, HDL and LDL), leukocyte and thrombocyte count and Apoe to get insight in the vascular risk factors that might be associated with microvascular function and to detect diabetes. Furthermore, if subject gives permission for taking additional blood, these samples will be used for discovery of novel biomarkers related to the vascular dysfunction seen in CAA. Studies will include identification of dysregulated pathways (inflammatory and oxidative stress pathways are of particular interest) at the gene and the protein levels. Focus will be on biomarkers for endothelial function (like VCAM, ICAM), blood-brain barrier integrity (MMP2, MMP9, s100b) and vascular mural cell function (for example PDGFR*). Results will be correlated with findings from ongoing RNA-sequencing project on post-mortem brain tissue. This pilot study on blood biomarkers is a first step before screening larger biobank samples like the ones from the EDAN study. This additionally taken blood can also be used in other scientific studies from one of our project-partners on biomarkers related to CAA, which are currently in development.

Study description

Background summary

In cerebral amyloid angiopathy (CAA) the toxic protein amyloid accumulates in the wall of the small blood vessels in the brain and repeatedly causes intracerebral hemorrhages, which leads to focal neurological deficits, dementia and eventually death. Sporadic cerebral amyloid angiopathy (sCAA) is a common cerebrovascular disease in elderly. Sensitive biomarkers to detect CAA in vivo are not yet available, but are important not only to diagnose CAA as an important cause of dementia, but also to decide on specific treatments, detect CAA formation as a consequence of treatment and for clinical trial design.

We want to fill this gap by developing new methods to demonstrate the effect of the accumulation of this protein in the blood vessels of the brains by looking for biomarkers with MR imaging.

Hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D), is an autosomal dominant condition in which excessive CAA, most severe in the occipital lobe, causes lobar hemorrhages and hemorrhagic infarcts already at a young age, followed by cognitive decline.
First indications and most severe manifestations of CAA in HCHWA-D are found in the occipital lobe. Provocation of neuronal activation by a visual task can be exploited to detect microvascular impairment. However, the use of visual activation to detect microvascular impairment can not give any information on the spreading of the disease to other brain areas.

Therefore, a CO2-challenge (normal breathing alternated with inhalation of 5% CO2) will be applied to target more specifically the functioning of the (micro)vascular bed in the whole brain. The analysis will not only focus on the relationship of the visual task with the global stimuli, but also the added value of providing whole brain coverage for these measurements of hemodynamic functioning.

To study the effect on the large blood vessels, measurements with transcranial Doppler echosound (TCD) will be performed under hyperventilation, normal breathing and inhalation of 5% CO2. The capacity to counteract the alterations in cerebral blood flow in response to fast changes in blood pressure14, the cerebrovascular autoregulation will be assessed with a stand-up test using TCD.

With these combined studies we can evaluate global and local cerebral perfusion changes at arterial and microvascular level respectively high temporal resolution TCD and more detailed MRI perfusion measurements in HCHWA-D. The possible insight into the cerebral manifestations of HCHWA-D is of great significance. This neuroimaging biomarker could provide an effective diagnostic tools that will allow detection of CAA during life, establish the contribution of CAA to cognitive decline and dementia and to facilitate potential future personalized therapy.

Study objective

The primary objective for this study is to evaluate the cerebrovascular reactivity of HCHWA-D patients:
1. To compare the (autoregulatory) function of small brain vessels in HCHWA-D patients with matched controls using the cerebrovascular reactivity to CO2 and visual stimulation measurement with MRI.
2. To assess the dynamic cerebrovascular autoregulation (dCA) and cerebral vasomotor reactivity (CVMR), which are major controllers of cerebral blood flow (CBF), using transcranial doppler (TCD) in the same groups.

Study design

This is an observational cross-sectional study comparing the cerebral autoregulation in symptomatic HCHWA-D patients with healthy age and sex matched controls. The controls will follow the same study protocol as the patients.

The first part of this study consists of a single MRI scan session with a 3 Tesla clinical MRI scanner consisting of different MR image types and cerebrovascular reactivity measurements with CO2 and visual stimulation.

In the second part of the study transcranial Doppler ultrasound (TCD) will be used to continuously measure the capacity to counteract the alterations in CBF in response to fast changes in blood pressure with a stand-up test (cerebrovascular autoregulation) and the vasodilatory response of the cerebral vessels to changes in arterial carbon dioxide concentration (cerebral vasomotor reactivity).

Blood will be sampled to get insight in the cardiovascular risk factors and cognitive tests will be performed.

All measurements are acquired in a single visit with a total duration of the session of approximately 6 hours, of which the MRI will take maximally 60 minutes and the TCD-measurement maximally 40 minutes. The participants will all be included at the LUMC. The duration of the study will be approximately 1 year and inclusion will start in Januari 2016.

Study burden and risks

MRI-scans will be made of the heads of the participants during challenges visual stimulation and low concentration CO2-inhalation. Before participation to the study the subject will be elaborately informed about the study and carefully screened for MRI-contraindications. The MRI-scans will be acquired by certified personnel of who at least one is an expert on CO2-reactivity scans.
In case a patient has migraine or epilepsy, the MRI part with the visual stimulus will be omitted from the protocol, because the bright flashing light could evoke an attack.
TCD-scans will be measured during challenges like standing up and low concentration CO2-inhalation. Earlier MRI- and TCD-studies with these low concentrations of CO2 in healthy subjects and patient populations did not show any adverse reactions. The risk of related to participation in this study will be minimal for the subjects.
Finally, the duration of the MRI-measurements will be restricted to a maximum of 60 minutes and TCD-measurements to a maximum of 40 minutes to limit the burden for the participants. There is no direct benefit for the participants, since currently there is no treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Symptomatic HCHWA-D patients:
* HCHWA-D with a genetic-based diagnosis
* One or more radiological confirmed hemorrhages
* Ability and willingness to provide written informed consent
* Age: older than 18 years;Control subjects:
* Age and gender matched with the HCHWA-D subjects, older than 18 years
* Ability and willingness to provide written informed consent

Exclusion criteria

* Presence of other known cerebrovascular diseases not related to CAA: diabetes,

hypertension, overt atherosclerotic disease
* Contra indications to MR imaging
* Contra indications to CO2 stimulation
* Severe physical restriction / inability to be scanned, such as weight above 120 kg.

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):	29-03-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	MRI and TCD scans with inhalation of low concentration CO2.
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	19-01-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-03-2016

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL54093.058.15