Vascular reactivity as a surrogate marker in CADASIL

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Primary Objectives: - To determine which technique is most optimal for measuring vascular reactivity in CADASIL patientsSecondary Objectives: - To study CADASIL disease progression over a 17- year time frame - To determine the correlation between...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON45639

Source
ToetsingOnline

Brief title
Vascular reactivity in CADASIL

Condition

- Central nervous system vascular disorders
- Vascular disorders NEC

Synonym
hereditary vascular dementia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Hersenstichting

Intervention

Keyword: CADASIL, Disease progression, Surrogate markers, Vasculair reactivity

Outcome measures

Primary outcome

Differences in vascular reactivity between CADASIL patients and controls

Correlation between vascular reactivity measurements and clinical severity

(scores on neuropsychological and disability scales, age at first stroke)

Correlation between vascular reactivity measurements and MRI parameters (number

of lacunar infarcts, brain atrophy)

Secondary outcome

Correlation between changes in vascular reactivity over a 17-year timeframe and

disease progression. Correlation between other candidate markers (skin NOTCH3

score, serum NOTCH3 levels) and disease progression.

Study description

Background summary

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a hereditary dementia and stroke syndrome, caused by mutations in the NOTCH3 gene. CADASIL patients typically suffer from mid-adult onset stroke and cognitive decline, leading to severe disability and dementia in generations of family members. There is no therapy for CADASIL. We have developed a potential therapeutic intervention for CADASIL patients, which is currently in the pre- clinical stage of development. An important bottle-neck in advancing therapeutic development is the lack of feasible read-outs. These read-outs are needed to enable assessment of therapeutic efficacy of any novel therapies in patients, especially in the early or pre-symptomatic stages of the disease. Therefore, for both CADASIL patients and their pre-symptomatic family members, development of surrogate markers is important in view of furthering the development of CADASIL therapeutics. A potential surrogate marker is cerebrovascular reactivity (CVR). CVR has previously been shown to be altered

in CADASIL patients, already in the early symptomatic stages of the disease. Moreover, CVR has been shown to correlate with disease severity, and to be predictive of disease progression. Therefore, CVR might be a candidate marker for potential future clinical trials in CADASIL, especially in pre-and early symptomatic patients. In this study, we determine which technique is most optimal for measuring vascular reactivity. Furthermore, we will assess the correlation between vascular reactivity and other candidate surrogate markers, and CADASIL disease progression.

Study objective

Primary Objectives:
- To determine which technique is most optimal for measuring vascular reactivity in CADASIL patients

Secondary Objectives:
- To study CADASIL disease progression over a 17- year time frame
- To determine the correlation between candidate surrogate markers (vascular reactivity, skin NOTCH3 score and serum NOTCH3 levels) and CADASIL disease progression

Study design

This study is a cross-sectional study of 16 CADASIL patients and 16 controls. We will ask individuals who participated in our baseline 2000 study (41 patients, 22 controls), to participate in the present study. This also provides the opportunity for a 17-year follow-up of the baseline 2000 cohort.

Study burden and risks

This is a group-related, non- therapeutic study in CADASIL patients. We will first include CADASIL patients and controls who also participated in the baseline 2000 study. In this way, we can do a sub-study with a unique 17-year follow-up analysis. All investigations will be performed during a one-day visit to the LUMC. Prior to the research day at the LUMC, patients will be asked to fill in a questionnaire. During the research day, maximum 60 ml of blood will be drawn, a skin biopsy will be taken, an MRI scan will be made (60 minutes), and participants will undergo neuropsychological testing (60 minutes). Acetazolamide will be administered intravenously during the MRI examination, to assess cerebrovascular reactivity. The risks of acetazolamide are minimized by excluding individuals which have a higher risk for an adverse reaction, and by consulting the LUMC pharmacy if participants are taking medications which are known to interact with acetazolamide. Overall the risks associated with this study are minimal. There is no direct benefit for the participants in this research. However, the knowledge obtained through this research is important for furthering the development of potential future therapeutic strategies for

CADASIL, and to get a better understanding of CADASIL disease course.

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

- participant in baseline 2000 study (P80/98)
- Aged above 18 years
- NOTCH3 mutation status known OR partner of a CADASIL patient

Exclusion criteria

contra-indication for MRI scanning:

- Claustrophobia
- Pacemakers or defibrillators
- Nerve stimulators
- Intracranial clips
- Intraorbital or intraocular metallic fragments
- Cochlear implants
- Ferromagnetic implants
- Hydrocephalus pump
- Intra-utrine device (not all types)
- Permanent make-up
- Tattoos above the shoulders (only those older than 20 years);Contra- indication for fMRI:
- Seizure within prior year.
- Non-correctable visual impairment.;Contra- indications for acetazolamide challenge:
- Steven-Johnsons syndrome
- Individuals from Japanese or Indian descent
- Known allergy to sulphonamides
- Known severe liver or renal insufficiency
- Known occlusion of the a. vertebralis, basilaris or carotis

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2017
Enrollment:	46
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-12-2017
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	NL61040.058.17