DiViNAS study (Disease Variability in NOTCH3 Associated Small vessel disease): the NOTCH3 mutation position effect and other disease modifiers in CADASIL

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Aim and Objectives The overall aim is to define the broad disease spectrum of cysteine altering NOTCH3 mutations, specifically the as yet unexplored milder end of this spectrum, and to determine to what extent the mutation position predicts disease...

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

Summary

ID

NL-OMON50750

Source
ToetsingOnline

Brief title
DiViNAS study

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Central nervous system vascular disorders

Synonym
hereditary vascular dementia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CADASIL, Disease modifiers, Mutation position, Surrogate markers

Outcome measures

Primary outcome

Measures of clinical severity:

- age at onset of first stroke, number of strokes

- scores on disability scales

- psychometric testing

MRI lesion load:

Brain imaging will be performed on a 3 Tesla MRI scan, including 3D high resolution T1-w, T2-w, SWI, DTI, MTR and FLAIR sequences. Main parameters will be brain volume, number of lacunes, lacune volume, number of microbleeds and volume of white matter hyperintensities.

Secondary outcome

Candidate read-outs:

- fMRI after visual stimulus (non-invasive measurement of cerebrovascular reactivity)

- NOTCH3 score in skin biopsy

- Blood biomarkers (e.g. NOTCH3 levels, neurofilament light chain levels, endostatin levels and other potential biomarkers)

Study description

Background summary

CADASIL is a hereditary dementia and stroke syndrome, caused by archetypal cysteine altering NOTCH3 mutations. LUMC is the national CADASIL expertise centre and next to patient care, the research group has set up a CADASIL registry and has been studying disease natural history and genetic intervention therapies amongst others. CADASIL has an estimated minimal prevalence of 2-5:100.000. However, we have recently discovered that archetypal CADASIL-causing NOTCH3 mutations have a prevalence of 1:300 in the general population worldwide (i.e. approximately 100 times more frequent than the estimated minimal CADASIL prevalence), suggesting that CADASIL is likely much more prevalent than previously suspected, implying that the disease spectrum must be considerably broader than recognised to date, with the majority of individuals not having a CADASIL diagnosis. Our hypothesis is that the NOTCH3 associated phenotype may have an attenuated form which may be much more common than *classical* severe CADASIL. We were indeed able to show that even within CADASIL samples, there are significant differences in disease severity, and that this partially explained by a hitherto unknown effect of the position of the mutation along the 34 epidermal growth factor-like repeat (EGFr) domains of the NOTCH3 protein. These new findings have important implications in our understanding of the NOTCH3/CADASIL disease spectrum, disease pathomechanism, disease modifiers and potential protective measures and future therapeutic targets. Firstly, our objective is to capitalize on our recent findings by performing the first prospective study of the NOTCH3 mutation position effect in a large (n=200) sample of CADASIL patients with specific inclusion criteria for mutation position. Secondly, our objective is to study a potential attenuated form of CADASIL by phenotyping elderly undiagnosed individuals harbouring NOTCH3 mutations in known CADASIL pedigrees. Thirdly, our objective is to investigate potential surrogate markers for disease severity, such as the NOTCH3 score we developed in our transgenic NOTCH3 mice, NOTCH3 levels in plasma, BOLD response with fMRI, neurofilament light chain levels in serum and endostatin levels in plasma.

Study objective

Aim and Objectives
The overall aim is to define the broad disease spectrum of cysteine altering NOTCH3 mutations, specifically the as yet unexplored milder end of this spectrum, and to determine to what extent the mutation position predicts disease severity.

Primary Objectives
1. To assess to what extent mutation position determines NOTCH3 disease

severity and what the additional effect is of other known modifiers, such as vascular risk profile.
2. To delineate the mildest end of the NOTCH3 disease spectrum by assessing clinical severity, the MRI and cognitive profile of 60+ year old individuals with a cysteine altering NOTCH3 mutation, but without a clinical CADASIL diagnosis.

Secondary objectives
1. Create a large baseline cohort with symptomatic and asymptomatic CADASIL patients that can be used in future follow-up studies, including biobanking.
2. Determine the correlation between candidate surrogate markers (e.g. vascular reactivity, skin NOTCH3 score and blood biomarkers) and CADASIL disease severity.
3. To acquire hiPSCs for in vitro modelling of CADASIL (vessel-on-a-chip), especially to investigate the molecular mechanisms underlying the NOTCH3 mutation position effect (collaboration with Prof. C. Mummery, dep. Of Anatomy and Embryology).

Study design

This is a non-intervention cross-sectional study including approximately 250 individuals with cysteine altering NOTCH3 mutations (CADASIL), recruited from the Dutch CADASIL registry.

Two cohorts will be included:
1. The NOTCH3 spectrum cohort
This is a cohort including CADASIL-patients aged 20 years and older; n=100 patients with an EGFr 1-6 mutation and n=100 individuals with an EGFr 7-34 mutation.

2. Elderly NOTCH3 sample
This is a sample of maximally 50 individuals, aged 60 years or older, harbouring a NOTCH3 mutation but without a prior CADASIL diagnosis.

The study will be performed in the LUMC at the departments of clinical genetics, radiology, neurology and dermatology. We aim to start the study in January 2019 and to complete the study in June 2020.

The main procedures the subjects will undergo are:
- neuropsychological test battery
- MRI
- Two skin punch biopsy
- Blood withdrawal

Study burden and risks

Patients will be invited for a half-day visit to the LUMC, all measurements will be performed during this visit. Prior to the research day, patients will be asked to fill in a questionnaire about their medical history. During the day the patients will undergo two 4 mm punch skin biopsy, blood withdrawal (maximum 70 ml), neuropsychological testing and a MRI scan.
The risks of MRI are minimal. Potential risks from the MRI study include movement of paramagnetic objects in the body. Furthermore, some subjects may feel claustrophobic in the restricted space of the MR scanner. Claustrophobia from the MRI scan will be reduced by explaining the nature of the scanner in detail before enrollment. At all times, the subjects can request to be removed from the scanner. The physician will assess whether there are risk factors for MRI, and decide whether or not the participant is allowed to go into the scanner.
During and after the neuropsychological examination, there may be temporary distress and fatigue. Skin biopsy is generally a safe procedure, and will be performed under local anesthesia. In rare cases, local inflammation at the biopsy site can occur. The biopsy site will be sterilized with alcohol to minimize the risk of infection. In conclusion, the overall risk of this study is minimal.

The study will not be directly beneficial for the patient, however through this study we will obtain important knowledge about CADASIL, where the whole population of CADASIL-patients can benefit from in the future. Firstly, validating and further delineating the mutation position effect and finding other disease modifiers will be important for predicting disease course in diagnosed CASASIL patients as well as in patients with a chance finding of a cysteine altering NOTCH3 mutation in whole exome sequencing or whole genome sequencing analysis for another indication. Secondly, delineating the mildest end of the NOTCH3 disease spectrum will possibly reveal important differences between severe and mild patient groups, and thus direct future research into protective measures and therapeutic targets. Thirdly, development of surrogate markers is crucial for novel CADASIL therapeutic development.

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

NOTCH3 spectrum cohort
Patients will be recruited from our CADASIL registry. In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Aged 20 years and older
- Has a known heterozygous cysteine altering NOTCH3 mutation
- Is able to travel to the LUMC
- Is able to give informed consent, Elderly NOTCH3 sample
Individuals will be recruited through CADASIL pedigrees and our CADASIL registry. In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Aged above 60 years
- Living independently (mRS <3)
- No prior diagnosis of dementia
- A proven cysteine altering NOTCH3 mutation or 100% risk of a cysteine altering NOTCH3 mutation based on position in the family tree.
- Is able to travel to the LUMC
- Is able to give informed consent

Exclusion criteria

- contra-indication for MRI scanning:
o Claustrophobia
o Pacemakers and defibrillators

o Nerve stimulators
o Intracranial clips
o Intraorbital or intraocular metallic fragments
o Cochlear implants
o Ferromagnetic implants
o Hydrocephalus pump
o Intra-utrine device (not all types)
o Permanent make-up
o Tattoos above the shoulders (only those older than 20 years), - Contra-indication for fMRI:
o Seizure within prior year.
o Non-correctable visual impairment.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-05-2019
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	14-03-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-08-2020
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	NL66056.058.18