Microvascular rarefaction in vascular cognitive impairment and heart failure - VCI

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

Summary

ID

NL-OMON54038

Source
ToetsingOnline

Brief title
CRUCIAL-VCI

Condition

- Central nervous system vascular disorders
- Cognitive and attention disorders and disturbances

Synonym
cerebral small vessel disease, vascular cognitive impairment

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: EU binnen het HORIZON 2020 programma

Intervention

Keyword: cognitive impairment, heart failure, microvascular rarefaction

Outcome measures

Primary outcome

• Advanced brain MRI markers for microvascular hypoperfusion and dysfunction:

-BBB leakage rate and fractional volume (DCE-MRI)

-grey matter perfusion (ASL-CBF)

-microvascular perfusion volume (IVIM)

-parenchymal diffusivity/microstructural integrity (IVIM)

-macrovascular perfusion (GE-DSC-MRI)

-microvascular perfusion (capillary transit time heterogeneity on GE-DCS-MRI or SE-DSC-MRI)

• Structural vascular markers: total brain volume, white matter hyperintensities volume, visual assessment of WMH Fazekas score, lacunes, microbleeds, perivascular spaces, total SVD burden score.28, 29

• Cognitive function: overall and domains of memory, information processing speed, executive function

Secondary outcome

VCI patients only

• Cardiac:

o echocardiography: Left ventricular (LV) end-diastolic and -systolic diameters, LV mass and the LV mass index, and left atrial volume and left atrial volume index, LV ejection fraction, global and regional longitudinal strain

o MRI: ejection fraction, diastolic volume, end systolic function, cardiac

output, left ventricular mass, diastolic function (early to late ventricular

filling ; E/A ratio), left atrial volume as measure for diastolic function.

Myocardial perfusion from the adenosine stress test.

o Serum markers of cardiac damage/strain (NT-proBNP, hs-TNT), fibrosis (PICP,

CITP:MMP-1) and inflammation (Gal-3, sST-2)

• Microvesicles: RNA content of endothelial derived microvesicles

• Vascular density on OCT angiography of the eyes

• Retinal vessel diameters and branching complexity measures (fundus imaging)

• Sublingual flow-related capillary density (GlycoCheck)

• Platelet hemostatic- and inflammatory function

• Tear fluid gadolinium

Study description

Background summary

Vascular cognitive impairment (VCI) is an umbrella term to cover all cognitive disorders from mild cognitive impairment through fully developed dementia that arise due to vascular dysfunction. Vascular dementia is the 2nd most common type of dementia after Alzheimers Disease. The vascular dysfunction in VCI is mainly due to cerebral small vessel disease (cSVD).
Heart failure with preserved ejection fraction (HFpEF) is diastolic heart failure where the heart muscle has stiffened and therefore doesn*t fill properly. About half of all patients with HF have HFpEF. It is a syndrome involving microvascular dysfunction due to small vessel disease.
The development of VCI due to cSVD and of HFpEF are both linked to the presence of comorbidities such as hypertension, diabetes, obesity and aging. Decreases in capillary vessel density within a tissue, called microvascular rarefaction, is a common feature of these comorbidities. For many of the comorbidities associated with HFpEF and VCI, capillary rarefaction actually precedes disease development. Significant evidence now suggests that capillary rarefaction may exacerbate or drive comorbidities. In mice, induced rarefaction through

muscle-specific ablation of VEGF resulted in a 45% reduction of insulin-stimulated whole-body glucose disposal during a euglycemic insulin clamp. The decreased capillary density was proposed to impede insulin delivery to muscles and adipose tissue leading to insulin resistance, a hypothesis that has been corroborated in humans. Hypertensive patients also have lower capillary density. Capillary rarefaction is present in young adults (23-33 years) with familial predisposition to hypertension that have yet to develop hypertension.
Microvascular rarefaction is now thought to be at the core of why small vessel diseases like HFpEF and VCI develop. Furthermore, cardiac microvascular disease leading to a failing heart (HFpEF) and altered cerebral function often present together. Disease progression in both HFpEF and VCI have been independently linked to microvascular function. Both organs are especially sensitive to the same types of insult. The brain and the heart have very high energy requirements. The brain uses approximately 1/5th of the body energy and the heart about 1/10th. Thus, reductions in perfusion in either organ are extremely detrimental. In patients with HFpEF, the degree of microvascular rarefaction correlates to the severity of left ventricular diastolic dysfunction. In VCI, although we are increasingly able to measure cerebral microvascular function, the knowledge about the role of microvascular function and rarefaction is sparse.
As a secondary aim, we are interested in the role of platelet function in cerebral small vessel disease. Platelets possess pro-inflammatory properties, but the role of platelets in the development of cerebral endothelial dysfunction is poorly characterized. We aim to characterize the interplay of platelets, endothelium and microvascular function in the development of small vessel disease.
As another secondary aim, we will investigate whether blood-brain barrier (BBB) leakage, one of the assumend pathophysiological mechanisms in cSVD, can also be detected by measuring gadolinium in tear fluid. There are some studies that suggest that gadolinium may leak over the blood-retinal barrier and can be found in ocular fluids, which may represent the eye involvement of cSVD. If so, collection of tear fluid could possibly offer an alternative, faster and cheaper way of assessing BBB leakage than MRI.

Study objective

The main objective of CRUCIAL-VCI is to determine a surrogate MRI marker for microvascular density in patients with VCI due to cSVD, and to relate this to disease severity expressed as macrostructural brain damage and cognitive function.
The secondary objectives are a) to investigate whether microvascular rarefaction is a specific feature of cSVD and not just an ageing phenomenon, by comparing VCI patients and healthy controls; b) to determine the relationship between cerebral microvascular function and (i) rarefaction in the heart and (ii) microvascular density in the eye and sublingual tissue; c) to identify and characterize mi-RNAs related to rarefaction from circulating endothelial

derived microvesicles and the correlation with cerebral microvascular function and structural MRI markers.

Study design

CRUCIAL-VCI is a single-center observational study.

Study burden and risks

The study requires a two-day visit to the hospital for VCI patients and a one-day visit for controls. Duration of the MRI to acquire all sequences is around two hours for VCI and one-and-half hours for controls. Venous injection of gadobutrol contrast agent can cause an allergic reaction, although this is very rare. Total dose of gadobutrol in controls is 0.2 mmol/kg and in VCI 0.3 mmol/kg. The latter dose is divided over two days. First day 0,2 mmol/kg and second day 0,1 mmol/kg and in no case the maximum daily dose of 0,3 mmol/kg will be exceeded. Blood samples will be taken by venous puncture. This may result in some cases in a cutaneous hematoma. Cognitive testing may tire. Collection of tear fluid can make the eyes dry temporarily (a few minutes to hours).

VCI patients only: ECG, echocardiography, sublingual Glycocheck are non-invasive and painless. OCT angiography of the eye requires administration of mydriatic eye drops for pupil dilation. This results in a blurry vision which lasts up to two hours. People are not allowed to drive during this period. Part of the cardiac MRI is an adenosine stress test. Participants are not allowed to drink coffee or caffeinated soft drinks in the preceding 12 hours. Injection of adenosine will simulate a condition of exercise. Adenosine administration is often accompanied by sensations of chest tightness, breathlessness and/or tachycardia. These sensations are harmless but might feel uncomfortable. If a person finds it too uncomfortable we will stop the infusion immediately and sensations will disappear shortly thereafter (T * <10sec). In general, the adenosine stress test is well tolerated and lasts only 4 minutes. It is a well-known test in clinical practise. Severe side effects such as severe bradycardia are rare and participants will be monitored continuously.

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

Inclusion criteria for VCI:
VCI due to cSVD defined as:
o visiting a memory clinic or outpatient clinic Neurology;
o cognitive complaints;
o demonstration of a cognitive deficit: MoCA less than 26 or impairment in at least 1 cognitive
domain in neuropsychological assessment
o imaging evidence of cerebral small vessel disease:
- extensive leukoaraiosis on CT, or
- (early) confluent WMH on MRI (Fazekas score >= 2), or
* - multiple punctate WMH on MRI in combination with lacunar infarcts or microbleeds.
o Age 18 years or older
o Ability to undergo MRI
o Capacity to give written informed consent
o Clinical dementia rating scale <=1

Inclusion criteria for patients at risk for VCI:
• Symptomatic cSVD, defined as:
o A history of a clinical lacunar stroke with a compatible lesion on CT or MRI (inclusion only > 3 months after stroke onset to avoid acute stroke effects)

o Additional imaging evidence of cerebral small vessel disease:
* extensive leukoaraiosis on CT, or
* (early) confluent WMH on MRI (Fazekas score >= 2), or
* Lacunar infarct in combination with multiple punctate WMH on MRI (Fazekas 1) or microbleeds.
• Age 18 years or older
• Ability to undergo MRI
• Capacity to give written informed consent

The controls are defined as:
- persons visiting the outpatient clinic Neurology
- complaints of the peripheral nervous system due to a.o. chronic polyneuropathy, ulnaropathy or carpal tunnel syndrome
- no cognitive complaints and/or symptoms
- age over 18 years
- Ability to undergo MRI
- Capacity to give written informed consent

Exclusion criteria

Exclusion criteria for both VCI and controls
• Inclusion criteria are not met
• Unwillingness or inability to give written consent
• mentally incompetent (or reasonable doubt about competence) to give informed consent
• Contraindications to MRI, among which: pacemaker, metallic foreign body, claustrophobia, pregnancy, neurostimulator, other kinds of implanted devices or insulin pump
• Contraindications to gadolinium contrast agent used for MRI, among which allergy or severe renal impairment (eGFR <30 ml/min)
• Other major neurological or psychiatric conditions affecting the brain and interfering with the study design, among which: multiple sclerosis, Parkinson*s disease, alcohol/drug abuse, major cortical stroke, major neuro-trauma, brain tumors

Exclusion criteria for cardiac MRI (VCI only)
• Asthma and/or COPD
• Slow heart rhythm (<50 beats per minute)
• AV-block II-III
• Sick sinus syndrome
• Prolonged QT-interval
• Hypotension defined as systolic blood pressure less than 90 mmHg
• Decompensatio cordis

Exclusion criterium for fundus imaging only (VCI group)

• epilepsy

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-12-2020
Enrollment:	115
Type:	Actual

Ethics review

Approved WMO Date:	16-07-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-05-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-01-2022
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-03-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	ISRTCN
CCMO	NL72696.068.20

Study results

Date completed: 08-10-2024

Summary results
Trial ended prematurely