Blood-brain barrier permeability in cerebral small vessel disease: a dynamic contrast-enhanced MRI study.

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1. Study the BBB permeability in cSVD patients and compare it with healthy control subjects. 2. Examine the relationship between BBB permeability and cognitive function. 3. Examine the relationship between BBB permeability and the extent of...

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

Summary

ID

NL-OMON41443

Source
ToetsingOnline

Brief title
Blood-brain barrier in cerebral small vessel disease

Condition

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

Synonym
Cerebral small vessel disease; disease of the small brain arteries

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,Mozaiekbeurs

verstrekt door NWO

Intervention

Keyword: Blood-brain barrier, Cerebral small vessel disease, Cognitive impairment, Lacunar stroke

Outcome measures

Primary outcome

BBB permeability, cognitive function, extent of structural lesions on MRI

associated with cSVD (WML, lacunar infarcts, BMB).

Secondary outcome

Sublingual glycocalyx thickness

Study description

Background summary

Cerebral small vessel disease (cSVD) is a disorder involving the small brain arteries. It is associated with structural lesions on brain MRI such as white matter lesions (WML), lacunar infarcts, brain microbleeds (BMB) and enlarged Virchow-Robin spaces. Clinically, cSVD is associated with diseases such as lacunar stroke (LACI) and vascular cognitive impairment (VCI). In addition, the radiological abnormalities of cSVD appear to be related to disease severity. Previous studies have shown that the extent of WML on brain MRI are related to the extent of cognitive decline. Furthermore, progression of WML correlates with progression of cognitive problems. Recent, preliminary studies have shown that the blood-brain barrier (BBB) may play a major role in the pathophysiology of cSVD. The BBB consist of different types of brain cells and endothelial cells. It forms a protective neuro-vascular unit for the brain by preventing harmful substances to leak out of the blood vessels into the brain tissue, and by establishing a stable micro-environment for the neurons. Dysfunction of the BBB however may lead to disruption of these protective mechanisms, resulting in aberrant angiogenesis, inflammatory reactions and changed transport of molecules between blood and brain. It is possible that this disruption plays a pivotal role in the pathophysiology of cSVD. However, up till now limited data are available on the role BBB in cSVD.
Furthermore, as cSVD is considered an endotheliopathy and alteration of the glycocalyx, a layer that covers the vascular endothelium, is associated with an

increased vascular permeability, it is possible that the glycocalyx is associated with BBB permeability in cSVD. However, the relationship between glycocalyx and BBB permeabiliteit has never been studied yet.

Study objective

1. Study the BBB permeability in cSVD patients and compare it with healthy control subjects.
2. Examine the relationship between BBB permeability and cognitive function.
3. Examine the relationship between BBB permeability and the extent of structural lesions on MRI associated with cSVD (extent of WML, number of lacunar infarcts and BMB).
4. Examine whether the degree of BBB permeability can predict future cognitive decline and/or progression of structural lesions on MRI.
5. Examine the relationship between BBB permeability and glycocalyx thickness in cSVD and healthy control subjects.

Study design

Prospective, observational, follow-up cohort study

Study burden and risks

Participants will receive structural brain MRI at two time points and one dynamic contrast-enhanced brain MRI (DCE-MRI), the latter requiring intravascular injection of a contrast agent for which the participant in rare cases can develop an allergic reaction. It is possible that participants will experience the MRI scans a uncomfortable due to the small space and the noise. In addition, participants will receive a neuropsychological assessment (NPA) at two time points, they will undergo a venipuncture for blood analysis once. Venipuncture may be experienced as uncomfortable and it may give the participant a temporary hematoma at the side of venipuncture. A glycocalyx measurement will be done once. This assessment does not have risks for the participants.

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

LACI patients: A first-ever acute lacunar stroke ;Mild VCI due to cSVD:
- Subjective complaints of cognitive functioning and objective cognitive impairment in at least 1 cognitive domain on cognitive testing, and
- A Clinical Dementia Rating <=1 and a MMSE >=20 (i.e. no dementia), and
- Vascular lesions on brain MRI (lacunar infarts, white matter lesions, deep microbleeds) that suggest a link between the cognitive deficit and cSVD.;Healthy control subjects: Healthy control subjects are included from the general population and matched to the LACI and mild VCI patients according to gender and age.

Exclusion criteria

Exclusion criteria for all subjects:
Cerebrovascular abnormalities in history
o Ischemic stroke
o Haemorrhagic stroke (subarachnoid or intracerebral)
Contra indications for MRI/DCE-MRI
o Heart valve prosthesis
o Pacemaker
o Intracerebral clips (aneurysm)
o Intra-ocular metal pieces
o Cochlear implant

o Claustrophobia
o Poor kidney function (GFR<30ml/min)
o Previous allergic reaction to contrast agent (gadobutrol)
Psychiatric disorders associated with (temporarily) cognitive decline (e.g. depression, psychosis);Group specific exclusion criteria:
Lacunar stroke
- Potential cardiac embolic source (e.g. atrial fibrillation)
- Stenosis of >=50% of one or both internal carotid arteries.
Mild cognitive impairment due to cSVD
- Clinical and/or subclinical cortical events
- Other causes for cognitive impairment (e.g. Alzheimers Disease)
Healthy subjects
- Clinically overt cardiovascular diseases
- Clinically overt cerebrovascular diseases
- Disease of the central nervous system (e.g. Multiple Sclerosis, brain tumor/metastasis)
- Extensive structural lesions on MRI associated with cSVD
- Cognitive impairment (i.e. objective and/or subjective cognitive deficits).

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:	Recruitment stopped
Start date (anticipated):	23-04-2013
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	01-03-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-04-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-09-2015
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

ID: 26559
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL41952.068.12
OMON	NL-OMON26559