Imaging NeuroVascular, Endothelial and STructural Integrity in prepAration to TrEat Small Vessel Diseases

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Primary objective:To determine BBB integrity and the interplay with microvessel function including PVS and CVR response to CO2 breathing challenge in sporadic and monogenic presentations of human SVDs.Secondary objective:To determine the…

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

Summary

ID

NL-OMON49782

Source
ToetsingOnline

Brief title
Investigate@SVDs

Condition

- Central nervous system vascular disorders
- Vascular hypertensive disorders

Synonym
Cerebral Small vessel disease, stroke and dementia

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: HORIZON 2020 studie gefinancierd door de

Europese Unie

Intervention

Keyword: Blood-brain barrier permeability, Cerebral small vessel Disease, Microvascular dysfunction, vascular inflammation

Outcome measures

Primary outcome

* BBB integrity as assessed using DCE-MRI brain scan

* CVR as determined by BOLD MRI brain scan response to hypercapnic challenge

(CO2 breathing as vasodilative stimulus)

* PVS score, count, and volume on structural MRI brain scan, assessed using

validated methods

Secondary outcome

* BP parameters (peak systolic, systolic, mean, diastolic arterial pressures,

pulse pressures, and variability)

* Systemic measures of vascular stiffness (PWV)

* CSF pulsatility as an index of rate of passage of pulse waves through the

brain (stiffness), measured using MRI brain scan.

* Structural MRI markers of SVD * WMH, PVS, lacunes, microbleeds, individually

and by total SVD score.

* Circulating immune cells identified by FACS analysis

Study description

Background summary

Cerebral small vessel diseases (SVDs) are a major cause of stroke and dementia, and yet there is no targeted treatment. Progress in understanding the mechanisms that drive microvascular dysfunction and brain damage in SVDs has been elusive, until now. Investigate@SVDs is part of a coordinated programme to elucidate key mechanisms common to different SVDs, and determine how these mechanisms contribute to individual SVDs (SVDs@Target Project, funded by the European Horizon 2020 Scheme).

Investigate@SVDs will assess factors that drive brain microvascular dysfunction in SVD. We will use MRI brain scans to assess microvascular function by measuring blood-brain barrier permeability, CVR, and cerebral pulsatility to understand the interplay of microvascular dysfunction and clinical and radiological features of SVD. Measurement of BPv over one week will help understand the role of the systemic circulation in the development of brain microvascular dysfunction. Finally, the role of vascular inflammation will be investigated by characterisation of circulating immune cells.

Study objective

Primary objective:
To determine BBB integrity and the interplay with microvessel function including PVS and CVR response to CO2 breathing challenge in sporadic and monogenic presentations of human SVDs.

Secondary objective:
To determine the relationship between BBB leakage and (i) BP and its variability and (ii) structural MRI markers of SVDs in sporadic and monogenic presentations of human SVDs.

Identification and characterization of circulating immune cells in sporadic and monogenic presentations of human SVDs and the correlation with BBB permeability, microvascular function and structural MRI markers.

Study design

Investigate@SVDs is an observational study

Study burden and risks

Participants will attend for two visits over a period of eight days. At the first visit, patients proceed to have a full medical history and examination performed, cognitive testing will be performed and blood samples will be taken for analysis Participants receive a BP machine to perform home BP monitoring with the device over the next seven days. Participants will attend for a second visit on day 7+/-1day and undergo brain MRI to measure BBB permeability, CVR and pulsatility of ICA and CSF flow. The total time to acquire all MRI sequences is around two hours. For the individual patient, participation in the study will have no direct benefit. In future perspectives, the results might advance our knowledge of SVD pathophysiology which can lead to better treatment options.

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 SVD defined as
- a history compatible with clinical lacunar stroke syndrome in the last 5 years with a recent small subcortical infarct visible on MRI scan or CT scan compatible with the clinical syndrome.
-or cognitive impairment defined as visiting a memory clinic and a clinical dementia rating score of * 0.5, and capacity to consent with confluent deep WMH on MRI (defined on the Fazekas scale as deep WMH score * 2).
- or a diagnosis of CADASIL established by molecular genetic testing of the NOTCH3 gene (presence of an archetypical, cysteine-affecting mutation) or the presence of granular osmiophilic material in ultrastructural, electron microscopy analysis of skin biopsy.
* Age 18 years or older
* Ability to undergo MRI
* Capacity to give written informed consent
* Independent in activities of daily living (Modified Rankin score <3)

Exclusion criteria

* Inclusion criteria are not met
* Unwillingness or inability to give written consent
* Pregnant or breastfeeding women, women of childbearing age not taking contraception.
* Contraindications to MRI: pacemaker, metallic foreign body (including aneurysm clip in the brain), claustrophobia, pregnancy, neurostimulator, pacemaker or other kinds of implanted devices or insulin pump.
* Contraindications to gadolinium contrast agent used for MRI
* Other major neurological or psychiatric conditions affecting the brain and interfering with the study design (e.g. multiple sclerosis)
* In case of clinical lacunar stroke syndrome other causes of stroke such as *50% luminal stenosis in large arteries supplying the area of ischaemia, major-risk cardioembolic source of embolism, other specific causes of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug misuse)
* Other stroke risk factor requiring immediate intervention that would preclude involvement in the study
* Renal impairment (eGFR <30 ml/min)
* Panic disorder

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-03-2018
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	02-02-2017
Application type:	First submission
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
ISRCTN	ISRCTN10514229
CCMO	NL58997.068.16