Do cerebral microbleeds in asymptomatic individuals reflect early CAA? The Early Detection of Angiopathy (EDAN) Study

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The general aim of this study is to implement validated markers for CAA in asymptomatic individuals with CMBs, to investigate whether presence of CMBs signifies early CAA.

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular haemorrhagic disorders
Study type	Observational invasive

Summary

ID

NL-OMON39566

Source
ToetsingOnline

Brief title
Microbleeds and early CAA

Condition

- Vascular haemorrhagic disorders

Synonym
cerebral amyloid angiopathy, protein accumulation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: asymptomatic individuals, cerebral amyloid angiopathy, microbleeds, neuroimaging

Outcome measures

Primary outcome

1) Measurement of cerebrovascular reactivity to physiological stimuli using fMRI.

Previous studies using functional transcranial Doppler (fTCD) to measure the flow velocity in the posterior cerebral artery after visual stimulation, showed a slower and lower peak response to visual stimulation in subjects with CAA compared to normal subjects. The preference of fMRI use over fTCD in this current study is due to less operator dependency and the additional spatial information fMRI provides.

2) PiB- retention measured in regions of interest.

PiB, a radioactive ligand, binds to vascular and plaque b-Amyloid. PiB-PET imaging is used to measure the PiB retention and distribution in regions of interests. Previous studies have reported on increased retention of PiB in non-demented subjects with CAA compared to normal controls. Retention was mainly seen in posterior brain regions, reflecting the predilection of CAA for the occipital cortex.

Secondary outcome

The assessment of the following neuropsychological tests will take place after fMRI; CAMCOG, MMSE, Wechsler memory test, trial making test, Stroop test, and

word learning test. Though both case and control subjects are neurologically asymptomatic and do not suffer from apparent cognitive impairment on study entry, these cognitive tests are applied in order to detect and adjust for subtle differences when present.

Study description

Background summary

Although it often goes unrecognized during life, cerebral amyloid angiopathy (CAA) is a common age-related brain pathology, with severe complications such as brain hemorrhage and dementia. CAA is a disease of the cerebral small vessels, affecting capillaries, arterioles, and small arteries of the cerebral cortex and leptomeninges and largely sparing vessels outside corticosubcortical regions such as basal ganglia and brainstem. The primary constituent of the vascular deposits is the ß-amyloid peptide. In moderate to severely advanced CAA, the vascular ß-amyloid deposits are accompanied by loss of vascular smooth muscle cells, microaneurysms, and paravascular accumulations of hemosiderin-laden macrophages, the pathological correlate of cerebral microbleeds (CMBs).

Radiographically, CMBs present as well-demarcated round hypo-intense lesions on magnetic resonance imaging (MRI). In CAA patients, microbleeds are almost invariably present in lobar brain regions. Yet, previous studies by our group have shown that CMBs - especially those in a lobar location- are also highly prevalent in neurologically asymptomatic individuals from the general population. Overall, microbleeds are present in up to 23.5% of persons aged 60 years and over, with more than half of these CMBs occurring in strictly lobar locations, i.e. locations suggestive of CAA. However, whether lobar microbleeds in these asymptomatic individuals indeed indicate CAA as underlying pathology remains unknown. Data from population-based autopsy studies suggest a high prevalence of preclinical CAA pathology of up to 50% in elderly persons, but there are to date no non-invasive studies during life to corroborate this. At present, neuroimaging markers to detect early CAA are being validated in well-defined patients with known CAA. We will apply these validated non-invasive markers to a group of asymptomatic individuals with lobar microbleeds, for whom the presence of CAA is uncertain. This will provide evidence whether microbleeds in asymptomatic persons may reflect early CAA.

Clinical- pathological correlation studies suggest that approximately 74% of lobar ICH and approximately 34% of all primary ICH in the elderly may be due to

advanced CAA. Overall outcome of lobar ICH is poor, with mortality ranging up to 30%, severe disability in approximately 40%, and recurrence rate of ICH of 20% in 2 years. Advanced CAA however is known to have a long prodromal phase, and it remains unclear if all individuals with early CAA will progress to advance CAA and eventually face clinical consequences. Therefore, identifying microbleeds as a potential MRI marker for early CAA would have implications to identify and follow up subjects with early CAA before clinical symptoms occur.

The primary focus of this current proposal is to investigate whether microbleeds in asymptomatic individuals reflect early CAA. We will do so by applying recently validated methods for detection of early CAA. Secondly, our results can be extrapolated to provide insight in the burden of early CAA in the asymptomatic elderly population. This is important information in light of ongoing investigations into prevention of CAA progression and CAA-related complications.

Study objective

The general aim of this study is to implement validated markers for CAA in asymptomatic individuals with CMBs, to investigate whether presence of CMBs signifies early CAA.

Study design

An observational cross-sectional diagnostic study

Study burden and risks

This is a non-therapeutic group relatedness study. Study enrolment indicates that participants will undergo fMRI, a PiB-PET scan, and a number of standardized cognitive tests. All tests have negligible health consequences. fMRI does not involve exposure to harmful radiation or other side effects in persons screened eligible to undergo MRI (without contra-indications). PiB-PET includes intravenous injection of radioactive 11-C-PiB ligand, which leads to a limited amount of radiation exposure, amounting to an effective radiation dose of 1.75 mSv (which is less than a year of background radiation). Contra-indications will be carefully investigated per subject to minimize the risks. Burden will be kept at a bear minimum by using short protocols.

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

1) One or more strictly lobar CMB on previously performed 3D T2*-weighted GRE MRI
2) Ability and willingness to provide written informed consent
3) Age >=60. There is no upper age limit or restriction on race or gender for study participation.

Exclusion criteria

1) Other definite cause of microbleeds of hemorrhage. Exclusion causes are excessive anticoagulation (INR >3.0), antecedent head trauma or ischemic stroke, CNS tumor, vascular malformation, vasculitis, and blood dyscrasia
2) History of symptomatic hemorrhagic stroke
3) Microbleeds outside lobar or cerebellar brain regions (e.g. basal ganglia, thalamus, brainstem) demonstrated by neuroimaging. The presence of additional cerebellar CMBs is not an exclusion criterium, as CAA can affect the cerebellum.
4) Dementia
5) Contra-indication to MRI (e.g. cranial metallic implant, cardiac pacemaker, severe claustrophobia)

6) Specific contraindications to fMRI, i.e.:
a. History of diabetes, ischemic stroke, transient ischemic attack, carotid/intracranial artery stenosis
b. Current tobacco use
c. Change in antihypertensive medication within the previous three months.
d. Seizure within prior year
e. Noncorrectable visual impairment

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2012
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO

Date:	29-01-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL41378.078.12