Cerebrovascular dysfunction in Alzheimer and mild cognitive impairment.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON30568

Source
ToetsingOnline

Brief title
Cerebrovascular dysfunction in Alzheimer and MCI

Condition

- Other condition
- Neurological disorders NEC
- Vascular disorders NEC

Synonym
alzheimer, dementia, mild cognitive impairment

Health condition

cerebrovasculaire dysfunctie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Internationale stichting alzheimer onderzoek ISAO

Intervention

Keyword: alzheimer, cerebral autoregulation, cerebrovascular, neurovascular coupling

Outcome measures

Primary outcome

Cerebrovascular recording methods

Neurovascular coupling studied with non-invasive Doppler-technique

Two 2 MHz-probes are mounted on an individually fitted headband. The P2-segment of the left posterior cerebral artery (PCA) and the right middle cerebral artery (MCA) are insonated. The recording of the MCA flow velocity allows determination for possible non-specific effects in the test situation such as blood pressure changes, which might affect cerebral circulation. Mean blood flow velocities are recorded using a Transcranial Doppler device (DWL, Singen, Germany).

As a stimulation parameter a colour movie is used. The visual stimulation protocol consists of 10 cycles each with a resting phase of 20 s (eyes closed) and a stimulating phase of 40 s. Changes between phases are signalled acoustically using a tone.

Beat-to-beat intervals of cerebral blood flow velocity are interpolated linearly for an averaging procedure. To assure independence from the insonation angle and to allow comparisons between the different participants, absolute

data are transformed into relative changes of cerebral blood flow velocity in relation to baseline. The baseline is calculated from the blood flow velocity averaged for a time span of 10 s before the beginning of the stimulation phase. The method and algorithm for analysing the data sets in terms of a control system are described in detail in Rosengarten (2001). The responses of the ten test sequences are averaged to improve signal-to-noise ration.

Cerebral autoregulation

The electrocardiogram (ECG) is measured by an in-home made portable ECG-amplifier. Arterial blood pressure (ABP) is measured using a non-invasive finger blood pressure monitor (Portapres, TNO) commonly used in studies on dynamic cerebral autoregulation. The cuff of the right size is placed on the middle finger of the left hand. A DWL Multidop Transcranial Dopplersonography device is used to measure the cerebral blood flow velocity (CBFV) in both the right and left middle cerebral artery (MCA). Two 2 MHz-probes are held in position by a special frame.

Data analysis

ECG, ABP and right and left-CBFV signals are recorded and on-line digitised and stored on a PC with an acquisition and analysis software package (AFO new version 2.33, developed by IDEE Maastricht). The sampling frequency is 250 Hz. An automatic algorithm detected R-waves from the ECG. Between every two R-waves the diastolic, systolic and mean values of the blood pressure waveform are determined. Correspondingly the peak-systolic, end-diastolic and mean CBFV

values are determined. Artefacts are removed by linear interpolation. The beat-to-beat values of ABP and CBFV are resampled at 5 Hz using spline-interpolation (8). From the ABP the mean value is subtracted and the CBFVs are normalised with respect to the mean. This results in zero-mean signals suited for spectral analysis to estimate the transfer function. The transfer function is calculated by

(1)

where Sxx(f) is the autospectrum of changes in arterial blood pressure and Sxy(f) is the cross-spectrum between the ABP- and CBFV-signals. The transfer function magnitude |H(f)| and phase spectrum *(f) are derived from the real part HR(f) and imaginary part HI(f) of the complex transfer function as

(2) (3)

The squared coherence function γ2(f) is estimated by (4)

where Syy(f) is the autospectrum of changes in cerebral blood flow velocity. The squared coherence reflects the strength of the linear relationship between ABP and CBFV for each frequency on a scale from 0 to 1.

PWV pulse wave velocity

Two pressure waves are recorded transcutaneously at the base of the neck for the right common artery and over the right femoral artery. PWV is determined as the foot-to-foot velocity. Pulse transit time was determined as the average of 10 consecutive beats. The distance travelled by the pulse wave is measured over

the body surface as the distance between the 2 recording sites. Aortic PWV is calculated as the ratio of distance to transit time.

PTT pulse transit time

PTT is the interval between ventricular electrical ECG activity (and arrival of a peripheral pulse waveform. It is the time needed for the pulse wave to travel from the aortic valve to the periphery, estimated as the delay between the R wave in the ECG (start Q-wave) and the arrival of the pulse wave at the finger as determined by finger finapres measurement.

Secondary outcome

results of neuropsychological tests performed before participation in this investigation.

results of cerebral neuroimaging (CT and/or MRI) performed before participation in this investigation.

Study description

Background summary

Brain function is critically dependent on continuous blood supply. Cerebrovascular dysregulation (CVD) can lead to brain dysfunction. Vascular factors are until recently not thought to play a role in Alzheimer*s disease (AD). However, an emerging view is that CVD may be a feature of AD. In AD, two control mechanisms, cerebral neurovascular coupling (NVC) and cerebral autoregulation (CAR) may be affected. NVC is a measure of brain blood flow changes in response to a stimulus (light, sound) and CAR keeps blood flow constant independent of blood pressure variations.

Study objective

Our working hypothesis is based on the interplay between vascular

dysregulation, neuropathological alterations and decline in AD brain function. In the latent phase vascular dysregulation is already apparent when patients are asymptomatic. Thereafter cognitive function begins to decline and neuropathological alterations become manifest. Cerebrovascular control (CVC) deteriorates in parallel with cognitive function. Major aim is to quantify NVC and CAR in AD and mild cognitive impairment (MCI) using non-invasive techniques. Also markers for possible systemic vascular abnormalities (pulse wave velocity, pulse transit time) will be studied. Recordings will be performed in definite AD, MCI and controls. Major objective is to verify the value of CVD testing as marker for early AD diagnosis.

Study design

It concerns an observational investigation in 3 groups namely 20 patients with probable or possible Alzheimer disease, 20 patients with mild cognitive impairment and a control group of 20. Among all participants investigations of the cerebrovascular and systemic vessels will be performed. The tests are visual neurovascular coupling, cerebral autoregulation, pulse wave velocity and pulse transition time.

In patients with AD measurements will be perfomed if possible before the patient is set on specififc anti-alzheimer medication. Use of medication is, for practicle reasons, no contra-indication.

Study burden and risks

Investigation load and risk for the participants are minimal. For the cerebrovascular tests the participant is lying supine in a bed. During the study of neurovascular coupling the participant has to actively view a dynamic visual stimulus during 40 seconds followed with an eyes closed period of 20 seconds. This sequence is repeated about 10 times.
All measurements are non-invasive, do not form a patient load and are painless.

Contacts

Public
Academisch Ziekenhuis Maastricht

P. Debyelaan
6202 az
Nederland
Scientific
Academisch Ziekenhuis Maastricht

P. Debyelaan
6202 az
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Alzheimer patients
Alzheimer diagnosed according to the DSM-IV criteria for dementia (American Psychiatric Association, 1994), and NINCDS-ADRDA criteria (McKhann et al., 1984)(probable, possible).
Presence of a reliable informant, who has contact with the patient at least once a week.
Informed consent of the patient before participation into the study.;MCI patients
The descriptions proposed by Petersen et al. (1999) are used to classify MCI.
Informed consent of the patient before participation into the study.;Controls
Informed consent before participation into the study.
Control matching parameters will be age, sex and level of education.

Exclusion criteria

Alzheimer patients
If living in a nursing home at the start of the study.
Patients without a reliable informant.
Diagnosis of Vascular Dementia, according to NINDS/AIREN criteria (Roman et al., 1993)
Presence of micro-vascular pathology as defined by the Fazekas scale (Fazekas, 1987)
Use of psychopharmacological medication.
Abuse of alcohol and/or drugs.
Diabetes
Heart disease
Presence of hypertension will be considered as a co-variate in the analysis.;To exclude patients with a possible stenosis (> 50%) of extra- and/or intracranial vessels a non-invasive

and non-aggravating standard duplex investigation will be performed in all subjects. Patients without a temporal *doppler* window will be excluded. In general about 1 out of 10 subjects will have no temporal window. According to this about 22 Alzheimer patients will have to be screened to acquire a group of 20 subjects.;MCI patients
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Controls
Use of psychopharmacological medication.
Abuse of alcohol and/or drugs.
Diabetes
Heart disease;To exclude participants with a possible stenosis (> 50%) of extra- and/or intracranial vessels a non-invasive and non-aggravating standard duplex investigation will be performed in all subjects.
Participants without a temporal *doppler* window will be excluded. In general about 1 out of 10 subjects will have no temporal window. According to this about 22 controls will have to be screened to acquire a group of 20 subjects
Control matching parameters will be age, sex and level of education.
Presence of hypertension will be considered as a co-variate.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2007
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	30-05-2007
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
CCMO	NL15574.068.07