Continuous CSF and plasma sampling method for amyloid biological variability in healthy volunteers and patients with Alzheimer*s disease.

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To explore diurnal fluctuation in CSF Aβ40, Aβ42, sAPPβ, t-tau and phospho-tau concentrations over 36 hours as well as cerebral production and clearance rates in healthy elderly volunteers and patients with mild stage of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Dementia and amnestic conditions
Study type	Observational invasive

Summary

ID

NL-OMON32144

Source
ToetsingOnline

Brief title
Alzheimer-liquor study

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer Disease, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W,Schering Plough company as investigator driven grant

Intervention

Keyword: Alzheimer, Amyloid-beta, Brain specific proteins, Cerebrospinal fluid

Outcome measures

Primary outcome

CSF and serum concentration of beta amyloid in time.

CSF and serum amyloid concentrations.

Secondary outcome

Tau and phospotau in CSF and serum in time

Study description

Background summary

Alzheimer*s disease (AD) is a neurodegenerative disorder characterized by the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) in cortical and limbic brain regions. Until now, during life only a "probable AD* diagnosis is possible, as based on clinical features and the results of neurological and neuropsychological testing. An accurate and early diagnosis is essential for appropriate support and treatment of dementia patients, since drugs for the symptomatic treatment of AD are currently available and drugs that may slow or halt the progression of the disease are being developed.
Given the favorable diagnostic accuracy to define or exclude the diagnosis AD amongst patients with dementia, CSF analysis of Aβ42, t-tau and p-tau proteins has obtained a position of growing importance in dementia diagnostics. Although much attention has been paid to pre-analytical (e.g. sampling and storage conditions) and analytical requirements (e.g. test characteristics), until recently little was known about fluctuations in concentrations of these biomarkers over time. Several studies showed that long-term fluctuations were minor, but recent studies in which CSF was collected hourly over a 36-hours period, demonstrated that diurnal fluctuations may considerably affect Aβ concentrations, with variations in the concentrations over 36 hours of at least a factor 2-3 . These studies suggested that the specific timing of CSF sampling is important in establishing Aβ concentrations. Further elaboration of these

diurnal variation is a necessary precondition to be able to implement the CSF measurements in clinical practice in memory clinics. Diurnal fluctuations have not been proven in Alzheimer patients, but if these are similar or larger, strict protocols should be used for CSF collection in order not to jeopardize valid interpretation of these tests. This clarifies the direct clinical relevance of this study: if the variability is too high the current clinical practice should absolutely change.

Study objective

To explore diurnal fluctuation in CSF Aβ40, Aβ42, sAPPβ, t-tau and phospho-tau concentrations over 36 hours as well as cerebral production and clearance rates in healthy elderly volunteers and patients with mild stage of Alzheimer*s disease. Furthermore, Aβ40 and Aβ42 plasma concentrations will be measured.

Study design

This study is a feasibility and reliability study to explore the cerebral specific proteins Aβ40, Aβ42, sAPPβ, t-tau and phospho-tau in CSF and Aβ40, Aβ42 in plasma. This study will be performed in the UMC St Radboud at the Department of Geriatric Medicine. 6 healthy volunteers and 6 patients with mild stage Alzheimer*s Disease (>= 50 years) will participate in the trial. All patients will undergo the same procedures.

Screening
From three weeks until 2 days before study start screening will be performed. The physician will check if the subject is eligible. Medical history, recent and current medication use will be recorded. General physical examination will be performed and height, weight, blood pressure, heart rate and body temperature will be measured. Furthermore, and ECG will be recorded and blood will be drawn. If the subject is a woman, she should be post-menopausal.

Hospitalization
When all screening results are available and the participant is eligible, the patient will be requested to be admitted to the hospital within 3 weeks after the screening visit. This admission will take approximately 3 days (60 hours). The participants are admitted on day -1 at around 20:00 and will be fasting from that time. Furthermore, blood will be drawn and an ECG will be recorded at day -1.
The participants will receive a spinal subarachnoidcatheter, to be inserted by anesthesiologist. Furthermore, the participants will receive an intravenous catheter in order to draw blood.
During the following 36 hours, spinal fluid and blood will be drawn every hour. In total approximately 216 ml of liquor and 216 ml of blood will be drawn during this period.
Furthermore, blood pressure, heart rate and body temperature will be measured

three times a day (in the morning, at noon and in the afternoon) at day 1 and 2.
After 36 hours the spinal and intravenous catheters will be removed. The participant will remain in the hospital for another 12 hours for observation.

Follow up visits:
An outpatient follow up visit and a follow up visit will be performed by phone on day 7 and day 30 respectively.

Study burden and risks

Due to insertion of the spinal catheter and liquor sampling, some people experience headache which can last for several days. Infection can occur at injection site or deeper (meningitis). Liquor leakage at catheter insertion site is possible. In order to minimize the risk of infection and other complications, the spinal catheter will be inserted under the aseptic conditions at the operation theatre by an experienced anesthesiologist (local anesthesia is provided). After removal of the spinal catheter, the participant will remain in the hospital for another 12 hours for observation.

Blood drawing can cause discomfort, such as pain or hematomas at the site of venapunction. Local blood clots and infections can occur, but this is rare. During hospitalization, during 36 hours blood and spinal fluid will be sampled every hour. The spinal catheter in the lower back en the intravenous catheter are inserted in such a way that the participant*s hindrance of repeated sampling is minimal.

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

ad 1. Healthy elderly volunteers, aged 50 yrs and over
ad 2. Patients 50 years or older with mild stage Alzheimer's disease (diagnosed accoring to the internationally accepted NINDS-ADRDA criteria, mild stage: CDR, clinical dementia rating = 1)

Exclusion criteria

1. Usage of:
a. Anticoagulants (low molecular heparines, acenocoumarol derivates),
b. thrombocyte aggregration inhibitors (acetylsalicylic acid, carbasalaat calcium, clopidrogel, dipyridamol)
c. NSAIDs that cannot be stopped during the study
2. allergy to epidural or other anaesthetics
3. intracerebral mass, as diagnosed by CT or MRI before the study
4. other neurological diseases
5. incapable to consent for the study (judged accoring to the procedure proposed by vd Vorm & Olde Rikkert, 2008, Competence assessment in Dementia; Springer Verlag, Wien; p 85-92)
6. Subjects with a contraindication for a spinal catheter

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:	Recruiting
Start date (anticipated):	05-01-2009
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	15-12-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL22274.091.08