Losing sleep over Alzheimer*s disease? Effects of sleep deprivation on cerebrospinal fluid amyloid-beta dynamics

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

Summary

ID

NL-OMON36421

Source
ToetsingOnline

Brief title
AWAKE

Condition

- Other condition

Synonym
Alzheimer's dementia, Alzheimer's disease

Health condition

neurodegeneratieve hersenaandoening

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,Alzheimer Nederland

Intervention

Keyword: Alzheimer's disease, Amyloid-beta, Cerebrospinal Fluid, Sleep Deprivation

Outcome measures

Primary outcome

In the intervention group CSF Aβ42 concentrations taken at 10 time points

before, during and after sleep deprivation, and in the control group at 6 time

points before and after the control night with unrestricted sleep.

Secondary outcome

-The concentrations of CSF Aβ40, t-tau, p-tau and hypocretin at 10 time points

in the intervention group and at 6 time points in the control group.

-The scores of continuous EEG measurements indicating quality of sleep and the

different sleep stages during the control night and registering if any sleep

occurred during the sleep deprivation night.

-Hemodynamic parameters, heart rate and beat-to-beat blood pressure for 5

subsequent minutes at 6 time points during the study.

Study description

Background summary

Alzheimer*s disease (AD) is a progressive neurodegenerative brain disease causing Alzheimer type dementia, the most common form of dementia. At present, 230,000 people in the Netherlands have AD and this number will rise to over

half a million by the year 2050. Existing therapies are, at best, symptomatic and do not prevent the progression of the disease. In order to develop more efficient, disease specific therapies and initiate treatment early on in the disease, the identification of factors contributing to the development of AD remains a very important goal.
AD is characterized by an increased production and decreased clearance of the amyloid-beta protein (Aβ) in the brain, forming plaques, and the formation of neurofibrillary tangles consisting of insoluble tau proteins. The cause of these neurodegenerative processes remains unclear and although multiple relating factors have been identified so far none can serve as effective biomarker for early detection or treatment.
One factor that seems to hold a relation to AD is sleep. For one, AD has proven to be associated with disruption of the sleep-wake cycle. In dementia patients partial restoration of a disturbed sleep-wake cycle, using both light therapy and melatonin, reduces cognitive decline. In recent animal studies a correlation between sleep-wake cycles and Aβ deposition has been established. Extended wakefulness was associated with increased production and subsequent deposition of Aβ. Sleep, in contrast, led to a marked fall in Aβ production. These findings indicate that sleep disturbance may in fact be one of the factors triggering overproduction and deposition of Aβ. If a similar relation between sleep disturbance and CSF Aβ levels can be demonstrated in humans, this may point out sleepdisorders as another risk factor profiling those at risk for AD.
A previous study performed at our department showed us that CSF AD biomarker levels can be measured regularly over a period of 36 hours using a spinal catheter. Here we will use this experience to measure CSF Aβ levels in relation to sleep deprivation.

Study objective

The primary objective is to determine an effect of sleep deprivation on CSF Aβ42 levels in humans.

Secondary objectives:
-Effect of unrestricted sleep on CSF Aβ42 levels.
-Effects of unrestricted sleep and sleep deprivation on other known AD biomarkers; Aβ40, t-tau and p-tau.
-Relation between the sleep regulatory peptide hypocretin and Aβ levels. In animal studies inhibition of hypocretin led to increased sleep and subsequently to reduced Aβ levels.

Study design

A randomized controlled study in 26 healthy, male volunteers, aged 40-60 yrs, of whom 13 will undergo a night of sleep deprivation (intervention group) and the other 13 a control night with unrestricted sleep (control group). CSF Aβ

concentrations will be measured before, during, and after the night of sleep deprivation and before and after the control night of unrestricted sleep.
Both in the intervention group and the control group CSF A*42 concentrations will be measured by collecting CSF with an intrathecal catheter, which will remain in place for 20 hours.

Study burden and risks

Complications related to the placement of the intrathecal catheter are leakage of CSF around the tube, kinking of the catheter, hematoma, CSF fistula, superficial infection and infections of the catheter which can lead to meningitis. These complications are rare and were not seen in our former study.
A complication of lumbar puncture that is more frequently seen is post spinal headache. However the risk of this complication developing with lumbar puncture is only 2.6%, according to a recent study in 1089 patients.
During a previous study at our department where during 36 hours hourly CSF samples were drawn, post spinal headache was seen in 8 out of 12 subjects. The intensity of the headaches varied but all were manageable with posture advice and painkillers. This complication was probably a results of the amount of CSF that was drawn, 216 ml over 36 hrs. Therefore, in the present study, in the control group there will be 6 moments of CSF sampling, with a total amount of 36 ml CSF drawn. In the intervention group there will be 10 moments of CSF sampling, with 60 ml of CSF drawn.
Sleep deprivation will lead to tiredness.

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

-Written informed consent
-Age 40-60 years
-Male
-Subject is in good health as established by medical history, physical examination, ECG and laboratory examination
-Laboratory parameters (as described on in section 3.7 screening) should be within the normal ranges as applicable in RUNMC, Nijmegen, or clinically acceptable to the investigator
-Normal sleep behaviour, Pittsburg Sleep Quality index score <=5
-MMSE 28 or higher
-Medication free

Exclusion criteria

-Presence of blood coagulopathy, established by medical history
-Allergy to local anesthetic agents
-Contra-indication for spinal catheter placement: medical history of compression of spinal cord, spinal surgery, skin infection, developmental abnormalities in lower spine
-Subjects who are currently participating in another study or have participated in a clinical study within 30 days, based on their own report about participation history
-Subjects with a history of drug or alcohol abuse in the past
-Subjects who are part of the study staff personnel or family members of the study staff personnel

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2011
Enrollment:	26
Type:	Actual

Medical products/devices used

Generic name:	Spinal Catheter
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	08-03-2011
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
Other	AWAKE32920
CCMO	NL32920.091.10