Glymphatic dysfunction in cognitive impairment: a memory clinic study

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON29030

Source
NTR

Brief title
GlyM

Health condition

Alzheimer's disease, Mild cognitive impairment

Sponsors and support

Primary sponsor: Maastricht University Medical Center
Source(s) of monetary or material Support: Alzheimer Nederland and MUMC+

Intervention

Outcome measures

Primary outcome

The primary endpoints are the interstitial fluid characteristics, the derived cerebral blood flow pulsatility index, and other derived MRI measures.

Secondary outcome

The cerebral blood flow pulsatility and ISF characteristics will be analysed as a determinant of cognitive function, day-to-day functioning, sleep behaviour, physical activity and MRI markers. The CSF or blood and tear fluid biomarkers will also be taken into account in when determining the relation of ISF characteristics, pulsatility and the structural and functional brain properties in patients.

Study description

Background summary

Alzheimer's disease (AD), the most frequent neurodegenerative disorder and most common cause of dementia in the elderly, is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles. Solute clearance in the brain is not only dependent on transport across the blood-brain barrier (BBB), but also on the clearance of interstitial fluid (ISF) in the brain tissue and the perivascular spaces by a waste clearance system, the so-called glymphatic system [1-3]. In addition is the brain highly vulnerable to the (kinetic) energy deposition of the arterial pulsatility which is increased due to the low resistance of brain arterioles and age-related hardening of arterial walls. Reduction in vascular elasticity and increased arterial pulsatility affect the perivascular clearance of waste products in the ISF [4], altering the physiologic transport of catabolites out of the brain including Aβ [2]. Therefore, a link between glymphatic function and AD has been hypothesized.

The number of patients with AD will increase dramatically in the upcoming decades [5]. The cause remains to be elucidated and effective options for treatment are therefore not yet developed. The current study aims to obtain a better understanding of glymphatic dysfunction in dementia of the Alzheimer's type and its preclinical stages. In addition, non-invasive imaging of the glymphatic system might provide an early biomarker of patients at risk (i.e. before the onset of overt symptoms).

Seven Tesla (7T) MRI provides high signal to noise and spatial details, and the unique opportunity to noninvasively assess various features of the glymphatic system by quantifying the volumetric fraction and dynamics of the ISF (using intravoxel incoherent motion imaging, IVIM) and measuring the pulsatility of small perforating lenticulostriate arteries (LSA) and other supplying arteries (using velocity sensitive MRI). We hypothesize that these features of glymphatic dysfunction can be linked to cognitive impairment. We will investigate the relationship between MRI-derived metrics indicative of the glymphatic system, namely interstitial fluid (ISF) characteristics and arterial pulsatility, with (1) brain tissue markers, (2) cognitive performance, and (3) AD biomarkers (Aβ/tau) in a memory clinic population.

The aim of this study is to discover how these metrics are affected in different stages of cognitive impairment. In a cross-sectional observational study, 120 individuals with different states of cognitive condition will be included. This will include 40 healthy cognitively normal controls, 40 patients with Mild cognitive impairment and 40 patients with mild AD dementia.

Study objective

1. Seven Tesla MRI can identify abnormalities of the glymphatic system associated with dementia and its preclinical stages relative to cognitively normal control (i.e. neurotypical) subjects.

2. More severe signs of dementia are associated with more affected glymphatic metrics: increased interstitial fluid fractions and arterial pulsatility are associated with neurodegeneration and more impaired cognitive performance.

Study design

One session at one time point

Intervention

Control subjects will undergo the following study specific measurements:
-the 7T MRI scan
-the blood pressure measurement
-questionnaires (CHAMPS, PSQI) and questionnaires on medical and demographic information
-neuropsychological testing
-blood sampling via venepuncture
-tear fluid collection

The participating patients (MCI and AD) will undergo the following study specific measurements:
-the 7T MRI scan
-the blood pressure measurement
-questionnaires (CHAMPS, PSQI).
For the participating patients (MCI and AD), information will be retrieved from the BBACL-cohort concerning neuropsychological test results, medical and demographic information, blood- and tear fluid measurements, and CSF measurements (if a lumbar puncture is performed for diagnostic purposes and CSF-values are registered within the BBACL).

Contacts

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Eligibility criteria

Inclusion criteria

Patients with mild Alzheimer's disease dementia, patients with mild cognitive impairment (MCI), and healthy subjects will be included.

In order to be eligible for the AD dementia-group, a subject must meet all of the following criteria:
- Mentally competent (MMSE≥18) and able to give informed consent
- Informed consent before participation in the study
- Age > 55 years
- Diagnosis of dementia of the AD type

Criteria for the MCI-group:
- Mentally component (MMSE ≥18) and able to give informed consent
- Informed consent before participation in the study
- Age > 55 years
- Diagnosis of MCI or diagnosis of Mild Neurocognitive Disorder (DSM V)

Criteria for the control (cognitively normal) group:
- Mentally component (MMSE ≥18) and able to give informed consent
- Informed consent before participation in the study
- Age > 55 years
- MMSE ≥ 26
- Average age and gender is similar to the patient groups

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Any significant disease or unstable medical condition that could influence neuropsychological testing (with the exception of a MCI or AD diagnosis)
- Major depression (according to the DSM IV) (< 12 months ago)
- Psychiatric history (schizophrenia, schizoaffective disorder, bipolar disorder or any history of electroconvulsive therapy)
- Vascular dementia
- Ischemic or valvular heart disease or electrocardiographic evidence of atrial fibrillation
- Recent transient ischemic attacks and ischemic or haemorrhagic stroke or cerebrovascular accident (< 2 years or paired with cognitive decline within 3 months after incident)
- Obstructive sleep apnoea syndrome

- Normal Pressure Hydrocephalus, M. Huntington, Parkinson’s disease, Frontotemporal dementia, Motor neuron diseases, Multiple sclerosis, Epilepsy
- Systemic inflammation, such as active rheumatoid arthritis
- Diabetes
- Cognitive impairment due to alcohol/drug abuse
- Structural abnormalities of the brain, such as tumours or stroke lesions
- Inability to provide informed consent
- Any contraindication for MRI: metallic implants, pacemaker, claustrophobia, pregnancy, tattoos in the head/neck region
- Unwillingness to be informed about potential abnormal MRI-findings

Additional exclusion criteria for the control group:
- A known diagnosis of mild cognitive impairment, prodromal dementia or dementia
- Substantial memory complaints (according to participant)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-07-2020
Enrollment:	120
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	24-07-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 56079
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8798
CCMO	NL72269.068.19
OMON	NL-OMON56079

Study results