Advanced MR Neuroimaging in presenile dementia

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The purpose of this research line is to assess whether measures acquired with advanced MR neuroimaging can be used as neuropathological markers for the early diagnosis of dementia and differentiation between AD and FTD. For each project, the...

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

Summary

ID

NL-OMON35133

Source
ToetsingOnline

Brief title
Functional imaging in presenile dementia

Condition

- Other condition
- Structural brain disorders

Synonym
dementia, MRI

Health condition

neurodegeneratieve aandoeningen

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: Alzheimer disease, Atrophy, Frontotemporal dementia, MRI, Perfusion

Outcome measures

Primary outcome

§ White and grey matter volumes.

§ White matter integrity: mean diffusivity (MD) and fractional anisotropy (FA)

maps.

§ Brain function: extent of fMRI activation (number and spatial distribution of

significantly activated voxels).

§ Quantitative brain perfusion maps.

Secondary outcome

na

Study description

Background summary

The two most frequent causes of dementia before the age of 65 years (ie, presenile dementia) are Alzheimer disease (AD, 35%) and frontotemporal dementia (FTD, 15%). Typically, patients with AD suffer mainly from memory disturbances, while in patients with FTD behavioural and language disturbances prevail. Diagnosis of dementia and differentiation between AD and FTD in the early stages of the disease may be difficult, as symptoms at this time may be mild and unspecific, and memory disorders may also be present in FTD. As yet, there is no diagnostic marker available to differentiate FTD from AD, and definitive diagnosis is commonly made in the later stages of the disease on clinical and neuropsychological grounds.
Differentiation between AD and FTD early in the disease is of clinical

importance for specific treatment and patient care strategies. Also, the long-term disease course is different between AD and FTD, and early diagnosis will provide patients and their family more certainty about the future in an early stage of the disease. Further insight into the neuropathological changes (atrophy, plasticity) occurring in FTD and AD may furthermore aid the future development of therapeutic strategies, while the same neuroimaging techniques can be used for treatment monitoring on a neurophysiological level.
Although AD and FTD affect different cognitive processes, in both diseases brain plasticity may compensate in the early stages of the disease (Yetkin 2006). This compensation explains why differentiation in the early stages of the disease based on clinical and neuropsychological findings is difficult: diagnosis only becomes apparent when the disease progresses and compensatory mechanisms fail.
On conventional magnetic resonance (MR) imaging, the hallmark of AD is atrophy of the hippocampus, which is often not present in the early stages of the disease, while it is also seen in advanced FTD. Imaging features of FTD are profound frontotemporal atrophy, which again only becomes prominent as the disease progresses and in the advanced stage may also be seen in AD.
Three advanced MR neuroimaging techniques hold promise for detecting changes in the grey and white matter integrity, brain function and brain perfusion before decrease in brain volume (atrophy) becomes visible.
With diffusion tensor imaging (DTI) the microstructure of the grey and white matter can be assessed noninvasively. An increase of mean diffusivity (MD) and reduction of fractional anisotropy (FA) indicate loss of parenchymal integrity, occurring prior to actual brain volume loss.
With functional MR imaging (fMRI), activity of the brain can be measured noninvasively. The compensatory processes that take place in the early stage of disease may be visualised as increased and more dispersed brain activation when compared with healthy controls. Such compensatory changes will be particularly apparent in the early stages of the disease, affecting preferentially those processes that are affected by AD and FTD. Conversely, once compensatory mechanisms fail, reduced activation is to be expected (Rombouts 2003). As memory disturbances are more prominent in AD and behaviour is more commonly affected in FTD, we will use an encoding and retrieval memory task and a social intelligence task respectively to engage these processes and study brain function in the early stages of the disease.
Arterial spin labelling (ASL) is a non-invasive MR imaging technique with which brain perfusion can be measured quantitatively. Hypoperfusion of specific brain areas in FTD and AD is a well-established finding in the advanced disease stages, and is traditionally assessed with positron emission tomography (PET) and single photon emission computed tomography (SPECT). ASL has several advantages over PET and SPECT imaging, in terms of its non-invasiveness, higher spatial and temporal resolution and quantitative properties. In advanced AD hypoperfusion is prominent in the parietal lobes, whereas the frontal lobes are affected in advanced FTD. Feasibility studies of ASL for assessing patterns of perfusion in these patient populations with advanced disease have shown patterns of hypoperfusion that are similar to those found with PET and SPECT

imaging (Johnson 2005; Du 2006). We will determine if this hypoperfusion is also discernable in early AD and FTD.

Study objective

The purpose of this research line is to assess whether measures acquired with advanced MR neuroimaging can be used as neuropathological markers for the early diagnosis of dementia and differentiation between AD and FTD.
For each project, the specific research questions are listed below.
Project 1 - diffusion tensor imaging (DTI):
1. Do patients with presenile dementia have different mean diffusivity (MD; increase) and fractional anisotropy (FA; decrease) of the hippocampus and the (normal appearing) white matter compared to healthy controls?
2. Are DTI measures (FA, MD) of the hippocampus and the (normal appearing) white matter early in the disease predictive of the definitive diagnosis of AD or FTD?
3. Do early changes in MD and FA predict atrophy (decrease in volume) of the areas predominantly affected in AD and FTD, namely the hippocampus, the frontal, parietal and temporal lobe?
Project 2 - functional MR imaging (fMRI):
4. Do patients with presenile dementia have different patterns of brain activation for memory encoding and working memory compared to healthy controls?
5. Are fMRI measurements of memory encoding and working memory early in the disease predictive of the definitive diagnosis of AD or FTD?
Project 3 - arterial spin labeling (ASL):
6. Do patients with presenile dementia have different brain perfusion (hypoperfusion) compared to healthy controls?
7. Are brain hypoperfusion patterns early in the disease predictive of the definitive diagnosis of AD or FTD?

Study design

Longitudinal case-control study.

Study burden and risks

none

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

- Young (<65 years) patients presenting to the memory clinic at Erasmus MC
- Suspected diagnosis of AD or FTD
- Mild dementia (clinical dementia rating scale <=1)

Exclusion criteria

- Contraindications for MRI scanning
- Inability to comprehend fMRI tasks
- Other causes of dementia (eg, vascular, alcohol, etcetera)
- Use of vasoactive or psychoactive medication

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):	01-11-2010
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	25-03-2010
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	NL28232.078.09