Frontotemporal Dementia Risk Cohort (FTD-RisC): Early biomarker abnormalities in patients with frontotemporal dementia

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Structural brain disorders
Study type	Observational invasive

Summary

ID

NL-OMON47834

Source
ToetsingOnline

Brief title
FTD-RisC study

Condition

- Structural brain disorders

Synonym
Alzheimer's disease, frontotemporal dementia, Pick's disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: NWO/ZonMw,aFTD;Stichting Dioraphte;Alzheimer Nederland

Intervention

Keyword: Biomarkers, frontotemporal dementia, MRI, presymptomatic

Outcome measures

Primary outcome

The main study outcome is the difference between persons with presenile dementia (FTD/AD), presymptomatic mutation carriers and controls using structural and functional connectivity MRI measures.

Secondary outcome

At baseline and the follow-up examinations we perform neuropsychological assessments. These neuropsychological tests can be correlated to the MRI results. Protein levels in CSF will be compared between patients, presymptomatic carriers and controls. Relatively new techniques, such as proteomics and microRNA sequencing, will be used to identify biomarkers in CSF and blood; these biomarkers will be compared between mutation carriers (presymptomatic versus symptomatic) and healthy controls.

Study description

Background summary

Frontotemporal dementia and Alzheimer*s disease cause most of the dementia cases in patients younger than 65 years. Often these diseases have insidious onset, and differentiation between the two diseases in an early phase can be difficult. With use of structural brain imaging such as magnetic resonance imaging (MRI) loss of brain tissue can be seen but this may be present only later in the disease process. Newer MRI techniques, such as resting-state fMRI (rs-fMRI), Diffusion Tensor Imaging (DTI) and Arterial Spin Labeling (ASL) may

show altered patterns even before apparent brain tissue loss on conventional imaging. In this project, we will study these patterns in patients with mild FTD, AD and presymptomatic persons who carry a gene mutation leading to FTD or AD. FTD can be caused by mutations in genes for microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9orf72). Early onset AD if often inherited in an autosomal dominant mode, linked to genetic defects in the APP, PSEN1 and PSEN2 genes. For upcoming medication trials, sensitive biomarkers to assess disease stage and track progression are needed. In order to investigate the effect of FTD/AD causing mutations on neural cells, neural cells can be derived from a skin biopsy (iPS cells). These IPS cells can be compared between patients with a mutation, healthy mutation carriers and persons without mutations. Subsequently, we can investigate the effect of a potential disease-modifying agent.

Study objective

The objective is to describe differences in MRI patterns in presymptomatic mutation carriers, patients with mild dementia and controls. We will study whether these patterns are specific depending on the type of dementia (FTD/AD) or mutation (GRN/MAPT/C9orf72). In addition, we will study whether even before clinical symptoms of dementia changes can be seen on MRI by investigating presymptomatic carriers of genetic mutations causing FTD or AD. By means of skin biopsy we can investigate the differences in neuronal cells. Furthermore, we aim to find biomarkers in blood and cerebrospinal fluid e.g. with the use of proteomics and miRNA techniques.

Study design

This is a longitudinal observational study over a period of five years with baseline and two follow-up visits (in case of two-yearly visits) or four follow-up visits (in case of yearly visits). Current participants will be asked to continue their study participation for another five years; i.e. three visits (in case of two-yearly visits) or five visits (in case of yearly visits). If the participants consents, a skin biopsy and LP will be performed. The LP can be repeated over time if the participant consents.

Study burden and risks

The participants will undergo fMRI scans and neuropsychological tests with no known health risks. They will have these examinations annually or two-yearly in a period of five years. They will have these examinations annually in a period of maximum five years. There is no direct benefit for the participants, but they will provide information on the most early brain changes occurring in brains affected by dementia. As such, participation will lead to a better understanding of the early phase of dementia. Future interventions will need to be given in the earliest phases of the dementia process, at a time when brain

tissue loss is not severe. An adverse event of vena punction includes the development of a hematoma. Adverse events of skin biopsy may include minor bruising or local tenderness at the site of venous blood sampling. All participants will be monitored to ensure proper hemostasis. There still is a lot of uncertainty about the risk associated with lumbar punctures. Contrary to popular belief, the risk is almost negligible. With the use of a thin, non-traumatic, needle the risk of a headache, which is the most common complication, is less then 10%. The quantity of liquor plays no role, as long as it is not more than 30 ml. Other complications such as meningitis and subdural spinal haematoma are very rare.

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

1) Patients with frontotemporal dementia referred to our referral center and diagnosed with use of International Consensus Criteria. The dementia symptoms have to be mild (clinical dementia rating <=1). Inclusion will be made when age of onset of dementia is below 65 year. Patients with all variants of frontotemporal dementia (behavioural frontotemporal dementia, semantic dementia, progressive non-fluent aphasia) will be included.
2) Patients with mild Alzheimer dementia diagnosed according to International Consensus Criteria. The dementia has to be mild (clinical dementia rating <=1). Inclusion will be made when age of onset of dementia is below 65 year.
3) Asymptomatic, first degree relatives of dementia patients due to genetic mutations. They have 50% chance of having the mutation and developing FTD. For the current study we collect new DNA and we will test them for the genetic mutation but keep them uninformed on the result unless they want to be informed. Participation is possible from 18 years and over.
4) Healthy persons who are age matched with persons having frontotemporal dementia.

Exclusion criteria

1) Patients with moderate to severe dementia (clinical dementia rating > 1).
2) Persons with a previous stroke or other (neurological) conditions that may affect cognitive functions (brain tumour, multiple sclerosis, use of psycho-active medications).
3) Contra-indication for undergoing MRI (pacemaker or other metal implants, claustrophobia, or unability to lie still for a period of 30 minutes in the MRI scanner).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	22-02-2010
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	28-12-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	12-08-2022
Application type:	Amendment
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	NL27885.078.09