Frontotemporal dementia Imaging of Neuroinflammation, Degeneration and Microglia-Related Effects

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

Summary

ID

NL-OMON49263

Source
ToetsingOnline

Brief title
FIND-MORE

Condition

- Structural brain disorders
- Dementia and amnestic conditions

Synonym
Frontotemporal dementia, FTD

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: [18F]DPA-714, Frontotemporal dementia, Microglia, Neuroinflammation, PET-MRI

Outcome measures

Primary outcome

The quantity and regional distribution of [18F]DPA-714 binding as a marker of microglial activation in patients with FTD compared to healthy controls.

Secondary outcome

- Comparison of [18F]DPA-714 binding between patients and presymptomatic gene carriers

- Comparison of [18F]DPA-714 binding between presymptomatic gene carriers and healthy controls (i.e. non-carriers)

- Correlation of [18F]DPA-714 binding with other MRI measures of neuroinflammation and neurodegeneration

- Correlation of [18F]DPA-714 binding with measures of clinical severity and neuropsychological performance

- Correlation of [18F]DPA-714 binding with levels of CSF and/or blood biomarkers

Study description

Background summary

Frontotemporal dementia (FTD) is the second most common early onset dementia (< 65 years), comprising various clinical, genetic and pathological subtypes. The age of onset, clinical presentation and disease course vary considerably, even within the same genetic or pathological subtype, which is largely unexplained until now. An emerging hypothesis is that neuroinflammation plays a role in the variability in clinical onset, clinical presentation and disease progression in

FTD. Increasing evidence from cellular, animal, and human postmortem studies points towards the involvement of microglia in the pathogenesis of FTD. However, only few studies have investigated microglial activity in vivo in FTD. Microglia can be visualized using PET imaging, specifically targeting markers of neuroinflammation such as the 18-kDa translocator protein (TSPO) receptor. The most widely used tracer for TSPO imaging so far has been the [11C]PK11195 tracer. The accuracy of this tracer is, however, limited due to poor bioavailability in the brain and low binding specificity for activated microglia. The second-generation tracer [18F]DPA-714 has improved bioavailability and binding specificity in the brain compared to [11C]PK11195, thus enabling a more accurate quantification of microglial activity. Due to these favorable properties, this tracer has been increasingly used for microglial imaging in clinical studies. The novel TSPO [18F]DPA-714 tracer has given promising results for the quantification of microglial activation in other neurodegenerative diseases, such as Alzheimer*s disease, multiple sclerosis and amyotrophic lateral sclerosis. To our knowledge, this tracer has never been used in FTD.
Our hypothesis is that in vivo imaging of microglia with the [18F]DPA-714 tracer will enable to visualize patterns of microglial activation in patients with FTD and to correlate them with clinical features and other disease markers (MRI measures, blood/CSF biomarkers, symptomatology, neuropsychological scores). This may help to better understand the role of microglia in the pathophysiology of FTD and onset of clinical disease, and to determine whether [18F]DPA-714 may be used as a diagnostic tool in FTD.

Study objective

Our primary objective is:
i. To assess the quantity and regional distribution of [18F]DPA-714 binding as a marker of microglial activation in patients with FTD compared to controls.

Our secondary objectives are:
i. To compare the quantity and regional distribution of [18F]DPA-714 binding in symptomatic and presymptomatic carriers of FTD genetic mutations;
ii. To explore the relationship between [18F]DPA-714 binding, clinical presentation and progression, and other markers of neurodegeneration (MRI, CSF/serum biomarkers).

Study design

We will perform a cross-sectional, observational study where individuals will undergo a diagnostic intervention, consisting of a single PET-MRI scan using the TSPO tracer [18F]DPA-714. The expected total duration of the project is two years; the project will last until the completion of the study procedures for the expected study sample.
Participants will be recruited from the Dutch FTD-RisC study cohort, which

includes more than 150 at-risk subjects from families with MAPT, C9orf72, GRN or TARDBP gene mutations. Additionally, we will invite sporadic FTD patients to participate in this study. These are patients that have been seen at the Alzheimer Center of the Erasmus Medical Center.
For the current study, individuals that are eligible will first undergo genetic screening to genotype the rs6971 polymorphism of the TSPO gene. This will enable us to determine binding affinity for the tracer. Next, high- and medium-affinity binders will be invited to undergo a single [18F]DPA-714 PET-MRI scan at the Erasmus Medical Center on a clinical PET-MRI scanner (GE Healthcare). All subjects will be required to sign informed consent prior to participation.
All patients will have a follow-up visit one year after the [18F]DPA-714 PET-MRI scan.

Study burden and risks

The overall risk associated with the study is estimated as low, and sufficient measures will be taken to deal with potential difficulties experienced by the participants. Idiosyncratic reactions to the tracer are unlikely. Pre-clinical testing of the tracer points to a favorable safety profile and a high margin of safety. Only mild transient side effects are observed in rats at doses 125 times higher than the maximal intended human dose. Further, other clinical studies used this tracer in humans successfully and reported no adverse effects. To deal with potential adverse effects during or directly after the scan, a physician will be present during the scanning procedures and will intervene if necessary. Further, in case of adverse effects occurring later, participants will be asked to contact a reference person among the investigators, and will receive the necessary medical help. The risks associated with the scanning procedures are rare and of minor severity. The radiation exposure is within acceptable limits. The scanning procedures may result in local side effects at the site of injection (e.g. pain, local hemorrhages, bruising, infection or blood clots), and in discomfort of the participants during the scan. Local side effects, if brought to medical attention, will be treated by a nurse or a physician as appropriate. The scan will be conducted with respect and care for the patient; the staff will provide clear instructions and support to make the participant at ease. If requested by the participant, the scanning procedures will be interrupted. An additional uncertainty is the possibility of incidental findings in the images. Incidental findings will be assessed by a competent clinical team to determine the clinical relevance. Clinically relevant findings will be communicated to the participant by his/her family physician.
The overall low risk is deemed acceptable when considering the expected benefits of the study, i.e. the discovery of important disease mechanisms that may lead to better diagnostics and therapeutic options targeting neuroinflammation in the patient population with FTD. FTD is a fatal disease, for which no cure is available. This is partly related to incomplete knowledge about disease mechanisms of neurodegeneration, and to the lack of reliable

biomarkers to track disease activity and predict the underlying pathology, which are needed to select patients for therapeutic trials. With this in mind, the current study attempts to expand the current state of knowledge on FTD pathogenesis, and to test [18F]DPA-714 PET as a potential diagnostic tool and disease biomarker.

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

- Able to tolerate the [18F]DPA-714 PET-MRI scan procedures and to make an informed decision to participate in this study
- Symptomatic patients must meet clinical criteria for FTD clinical syndromes
- Presymptomatic individuals and healthy controls must show no objective

evidence of cognitive impairment

Exclusion criteria

- Has contraindications for MRI scanning, e.g. metal objects in the body, claustrophobia
- Has evidence of structural brain abnormalities that are likely to interfere with the interpretation of PET scan
- Has one or more comorbidities that may interfere with the outcomes of the study (e.g. significant immune disease, neurological disease, CNS malignancy)
- Has a history of moderate or severe traumatic brain injury
- Has made use of immunomodulatory or immunosuppressive therapy in the 3 months prior to the scan
- Has any disease or uses medication that may compromise the function of the body systems and could interfere with the metabolism of the radiotracer or the interpretation of the results
- Has an unstable medical condition
- Is pregnant or breastfeeding
- Has a history of severe drug allergy or hypersensitivity
- Has been injected with a previously administered radiopharmaceutical within 6 terminal half-lives OR when the total yearly radiation exposure exceeds 10 mSv if participating in this protocol
- Is a low-affinity binder for the tracer based on the rs6971 TSPO polymorphism
- Has a present or past history of alcohol and/or drug abuse
- Makes use of benzodiazepines and is not able to suspend their use during the week prior to the PET scan

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	08-09-2021
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	-

Ethics review

Approved WMO Date:	08-10-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2020
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
EudraCT	EUCTR2020-002672-12-NL
CCMO	NL73807.078.20