Clinicopathological MRI and CSF correlates of iron accumulation, neurodegeneration and neuroinflammation in Huntington*s disease.

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1. To quantify brain iron accumulation in patient with HD using quantitative susceptibility mapping (QSM) at ultrahigh field (7T) as compared to healthy controls (case-control design).2. To link QSM results with specific and well-known clinical CSF...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON54707

Source
ToetsingOnline

Brief title
MRI and CSF pathological correlates in HD

Condition

- Neurological disorders congenital
- Neurological disorders NEC

Synonym
Huntington's disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZONMW grant,EHDN;LUMC

Intervention

Keyword: Cerebrospinal fluid, Iron, MRI, Neuroinflammation

Outcome measures

Primary outcome

The main study parameter are the striatal and cortical QSM measures, in

combination with CSF markers for iron, neurodegeneration and neuroinflammation,

in een Huntington populatie, in vergelijking tot gezonde controle deelnemers.

Secondary outcome

- Outcome measurement of clinical (neurologisch and psychological) and genetic

tests and their correlation with iron accumulation.

- Neuroinflammation metabolites, levels and characteristics, as measured with

(DW-)MRS iin combinaties with QSM measures en neuroinflammation - biomarkers in

CSF, in a Huntington's Disease population, as compared with healthy controls.

Study description

Background summary

Huntington's disease (HD) is a rare autosomal dominant inherited progressive neurodegenerative disorder caused by a pathological cytosine-adenine-guanine (CAG) repeat expansion within exon 1 of the Huntingtin (HTT) gene on chromosome 4. The disease typically manifests at a mean age at onset of 30-50 years and is characterized by a variety of motor disturbances (typically chorea and dystonia), cognitive impairment and behavioural changes.

Neurodegeneration in HD is a direct result of the CAG repeat expansion, which results in intracellular aggregation of the mutant huntingtin protein (mHTT),

thereby causing neuronal dysfunction and neuronal loss of the medium spiny neurons of the striatum. In addition to the well-documented neurodegenerative aspect of HD, strong evidence suggests a significant role for both iron accumulation and neuroinflammation, two mechanisms that often go hand in hand. MRI has been extensively used to visualize brain iron accumulation based on tissue susceptibility effects on T2*-weighted MRI images showing increased iron values in patients with HD.

Technical limitations of these imaging methods limit their sensitivity and specificity to disease*related tissue iron changes. The recent development of quantitative susceptibility mapping (QSM) overcomes these technical difficulties, providing a direct measure of tissue magnetic susceptibility. QSM has been shown to correlate linearly with the tissue iron content in gray matter, with high sensitivity and specificity to tissue iron changes, as demonstrated by post-mortem studies.

However, no study in any neurodegenerative disease so far has linked the observed increase of brain iron accumulation as measured by QSM with direct, well-established clinical measures for iron accumulation as cerebrospinal fluid (CSF). Moreover, previous studies focusing on iron accumulation in neurodegenerative diseases as Alzheimer*s disease as well as HD have shown that iron appears to be taken up by activated microglia, the resident macrophages of the brain. It is therefore thought that cerebral iron-accumulation in humans is mostly explained by iron-accumulating microglia in affected brain regions, linking iron to inflammation, a key pathological mechanism. Also here, no study so far has linked between brain iron accumulation and well-established CSF markers for neuroinflammation in HD.
We will also investigate the pathomchanism of neuroinflammation with MRI-scans, using (Diffusion Weighted)-Magnetic Resonance Spectroscopy (DW-MRS). With these method we can measure levels and compare characteristics of metabolites which are specifc for neuroinflammation.

As both iron and neuroinflammation are known to be involved in HD pathogenesis, iron imaging using QSM might be a potential imaging biomarker for disease state in HD possibly reflecting neuroinflammation in HD.

Study objective

1. To quantify brain iron accumulation in patient with HD using quantitative susceptibility mapping (QSM) at ultrahigh field (7T) as compared to healthy controls (case-control design).
2. To link QSM results with specific and well-known clinical CSF markers for iron, neurodegeneration, and neuroinflammation.
3. To quantify levels and characteristics of neuroinflammation metabolties, using (Diffusion Weighted-)Magnetic Resonance Spectroscopy ((DW-)MRS).
4. To link QSM results with neuroinflammation metabolites, using (DW-)MRS.
5. To investigate the relationship between brain iron accumulation as detected

by QSM and clinical and genetic characteristics of HD, assessed with valdiated scales, formulas and tests, to assess quality of biomarker for disease state, progression and ability to predict disease progression.
6. To follow-up these markers, using MRI and CSF, two years after baseline, to conclude if they change during disease progression and aging. This is of utmost importance, since an ideal biomarker should change along disease progression.

Study design

We will perform an observational cross-sectional and longitudinal study in a cohort of HD patients and age and sex matched control subjects. This study will take place in the LUMC. The cross-sectional part contains a two day visit for each participant and will include the following procedures: a 7T MRI scan of maximal 60 minutes, short motor, cognitive, psychological and functional assessments (45-60 minutes), a lumbar puncture and blood tests.
One year later we will follow-up the participants clinically, by assessing the same neuropsychological tests and neurological examinations as on Baseline. This visit will take 2 hours at the maximum and can be combined with other reasons for visiting the LUMC, like participating in the Enroll-study or seeing the neurologist for a yearly check.
Two years after baseline, the participant will be followed-up using the same assessments as they had during baseline: a 7T MRI scan of maximal 60 minutes, short motor, cognitive, psychological and functional assessments (45-60 minutes), a lumbar puncture and blood tests. These assessments will be obtained during a two day visit, like during baseline.
Three years after baseline the participant are invited for another clinical follow-up, in which the same neuropsychological tests and neurological examinations are assessed as during the first follow-up. This visit will take 2 hours at the maximum.

Study burden and risks

This is a non-therapeutic group relatedness study. The study day consists of a 7T MRI scan, which has no consequence for the health of the participants. In addition, a lumbar puncture will be performed. If the participant is in a good position, with head, neck, arms, and legs flexed as much as possible and if the participant has a normal anatomy of the vertebrae, a lumbar puncture is a minimal burdening to participants. Contra-indications for both MRI and lumbar puncture will be carefully checked per subject to minimize the risks. Burden will be kept at a minimum by using short protocols and breaks in between.

The ultrahigh field MRI system is widely used in research setting and since its first introduction in the 1990s no SAEs have been reported. Important temporary side-effects are vertigo, nausea and involuntary eye motion due to forces on ion currents in the semicircular loops. All individuals entering the 7 T MRI

are provided adequate sound protection to reduce the acoustic noise for protecting the ears and increase patient comfort during MRI. Since magnetic metal is attracted by the static field of the 7 T MRI a safety screening questionnaire determines whether it is safe for the patient to have the MRI. The Investigational Medical Device Dossier (IMDD) describes the risks analysis in more detail.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Male and female individuals with an age of 18 years and older; Ability to undergo MRI scanning; For individuals diagnosed with HD, a positive genetic test with a CAG repeat expansion of > 36 in the HTT gene is required; For pre-manifest participants a positive genetic test with a CAG repeat expansion

of >= 40 in the HTT gene is required.

Exclusion criteria

Contra-indications to MRI scanning and lumbar puncture; Pregnancy; Severe chorea; Inability to understand the information about the protocol; Severe physical restrictions.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-08-2021
Enrollment:	90
Type:	Actual

Medical products/devices used

Generic name:	MRI scanner
Registration:	No

Ethics review

Approved WMO

Date:	12-08-2019

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO Date:	03-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO Date:	26-08-2022
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Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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	NL69122.058.19