[LONGPDE10] Follow-up measurement of brain phosphodiesterase 10 A (PDE10A) enzyme levels in Huntington*s disease gene expansion carriers, 18 to 28 months after initial PET measurement in CHDIKI1201/PET-HD-PDE10A

Published: 04-04-2016
Last updated: 17-04-2024

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

Summary

ID

NL-OMON43581

Source
ToetsingOnline

Brief title
Longitudinal PET study PDE10A

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
neurodegenerative movement disorder

Research involving
Human

Sponsors and support

Primary sponsor: CHDI foundation
Source(s) of monetary or material Support: CHDI Foundation;USA

Intervention

Keyword: Huntington's Disease, longitudinal, phosphodiesterase 10 A (PDE10A) enzyme levels, positron emission tomography

Outcome measures

Primary outcome

The primary outcome measure will be the longitudinal change in binding

potential (BPND) estimated with the Logan graphical analysis using the

cerebellum as reference region.

Secondary outcome

The correlation between longitudinal changes of PDE10A enzyme availability

(BPND) and longitudinal changes of clinical ratings (stage and UHDRS, total and

subscores), and psychiatric and cognitive assessments.

Cognitive/behaviour scales to be used:

* From REGISTRY or ENROLL-HD:

o PBA-S (Appendix A)

o Cognitive Assessments: Verbal Fluency (letters), Verbal Fluency (Category),

Stroop (colour naming, word reading, interference), Symbol-Digit.

(Appendix B)

o UHDRS (Appendix C; for TMS and TFC)

* Not in REGISTRY or ENROLL-HD:

o MOCA (Appendix D)

The correlation between longitudinal changes of PDE10A enzyme availability (BPND) and the number of CAG repeats and disease duration (the classical definition of time when motor clinical manifestation first became noticeable will be used; applicable only in case of stage 1 and stage 2 subjects).

Study description

Background summary

Huntington*s disease (HD) is a neurodegenerative disorder characterised by progressive loss of the medium-sized spiny neurons in the striatum and by the development of chorea, psychiatric symptoms and cognitive deficits. The disorder is inherited as autosomal dominant disease and is characterised by the expansion of the CAG (codon that codes for the amino acid glutamine) repeat beyond the normal 10-35 repeat range in the IT15 gene encoding for the protein huntingtin . The hallmark of the disease is the accumulation of aggregates of mutated huntingtin, which has been found to impair cyclic adenosine monophosphate (cAMP) signalling and gene transcription mediated by the cAMP responsiveelement binding protein (CREB) . Phosphodiesterase 10 A (PDE10A) is an enzyme which is highly enriched in the medium-sized spiny neurons of the striatum and has an important role in the regulation of cAMP and cyclic guanosine monophosphate (cGMP) levels. Target genes of CREB include those responsible for neurotransmitter synthesis, release and signalling pathways , and also the brain derived nerve factor . Inhibition of PDE10A by inhibitors such as TP10 has been found to decrease neurodegenerative changes in the striatum of animal model of HD and restore cAMP dependent CREB signalling , . In animal models of HD it has also been found that changes of the levels of PDE10A occur also before the onset of motor dysfunction , suggesting that in Huntington*s Disease Gene Expansion Carriers (HDGECs) this abnormality can be present even before neurodegenerative changes take place and before the onset of clinical symptoms. Reduced levels of PDE10A messenger ribonucleic acid (mRNA) and protein have been found also in homogenates from the striatum of HDGECs . Inhibitors of PDE10A are now under clinical investigation for application in schizophrenia and might also be useful for the treatment of HD in which psychiatric symptoms also are prevalent.
In vivo imaging of PDE10A is at present possible using positron emission tomography (PET). A recent study with the PDE10A radioligand [18F]JNJ42259152 has reported a statistically significant difference in enzyme availability in HD patients compared with controls by 71% in the caudate and by 63% in the

putamen (10). [18F]MNI-659 is a radioligand for PDE10A developed at Molecular Neuroimaging; their recently published data in a small cohort of 11 HDGECs suggest that [18F]MNI-659 has the potential to serve as a striatal imaging biomarker (11). Initial data from the study CHDIKI1201/PET-HD-PDE10A show that the PDE10A enzyme is markedly affected in stage 1 and in late pre-manifest HDGECs (12). In stage 1 HDGECs compared to controls, striatal volumes, dopamine D2 receptor (D2 receptor) and PDE10A availability were 62±5%, 62±12%, and 21±33% of age-related control values ($p<0.05$). In late pre-manifest HDGECs compared to controls striatal volumes, D2 receptor and PDE10A availability were 80±18%, 72±12% and 53±22% of control values ($p<0.05$, except for nucleus accumbens volume). The REGISTRY study is a European study collecting prospective data on the phenotypical characteristics of HDGECs and individuals that are part of an HD family. The aims of the REGISTRY study are to investigate the course of the disease, genetic factors, and biomarkers. REGISTRY can also facilitate identification and recruitment of HDGECs to clinical studies and trials. The REGISTRY study is performed by the European Huntington*s
Disease Network (EHDN). A similar observational study to REGISTRY, by the name of ENROLL-HD has been set up with a more global reach than REGISTRY. ENROLL-HD has similar aims to REGISTRY and sites are currently being transferred one by one from REGISTRY to ENROLL-HD as they are granted appropriate ethical and other necessary approvals. It is anticipated that HDGEC recruiting sites on this study may transfer to ENROLL-HD during their participation in the study. The HDGECs recruited into this study will therefore have completed the previous PET study CHDIKI120/PET-HD-PDE10A and will be participating in either the REGISTRY or ENROLL-HD study. CHDI is the funding organization for the REGISTRY study and the sponsor for the ENROLLHD study.

Study objective

The primary objective is to measure the longitudinal changes of PDE10A enzyme availability in the caudate, putamen, and globus pallidus of Huntington*s Disease Gene Expansion Carrier (HDGECs) by comparison of the follow-up and initial Positron Emission Tomography (PET) measurements.
The secondary objectives are to:
1) Examine the correlations between longitudinal changes of [18F]MNI-659 binding potential (BPND) and longitudinal changes of clinical parameters
2) Compare the longitudinal changes of [18F]MNI-659 BPND between all HDGECs stages studied.

Study design

The study will be a follow-up, examining HDGECs at different stages of the disease (early and late pre-manifest, stage 1 and stage 2).The follow up PET measurement can be performed from 18 to 28 months after the initial PET measurement, with the aim of performing the follow-up PET measurement between

18-20 months after the initial PET measurement. The HDGECs (pre-manifest and manifest) included in this study will be recruited from the subjects that completed study CHDIKI1201/PET-HD-PDE10A. There will be a maximum of 45 HDGECs in the study.
The HDGECs will perform 2 study visits; Visits 1 (screening) and Visit 2 (PET) and 2 telephone follow ups, one after Visit 1 (telephone follow-up after screening) and one after Visit 2, (telephone follow-up after PET) during a maximum of 97 days.
The study will be conducted at the same recruiting centres in 4 recruiting countries for HDGECs (Sweden, Denmark, Norway, and the Netherlands) which participated in study CHDIKI1201/PET-HD-PDE10A.
There is one imaging centre: KI PET Centre, Stockholm, Sweden.

Study burden and risks

The radioligand [18F]MNI-659 will be administered at doses less than 5 micrograms, within the microdosing concept, and no pharmacological effects are expected. As of 31 October 2014 in study CHDIKI1201/PET-HD-PDE10A [18F]MNI-659 has been administered to 18 healthy controls, and 27 HDGECs at the PET Centre, Karolinska University (KI) Hospital, SE-171 76 Stockholm, Sweden, without any safety concern. In this study the injected radioactivity of [18F]MNI-659 will be similar to the baseline assessment, namely 185 MBq/70 kg of body weight ±10%. The effective dose for the injection of [18F]MNI-659 is approximately 5.6 mSv (approximately 2 years of background radiation in Sweden) for an average person weighing 70 kg. The total cumulative radiation dose the HDGECs will receive over 18-28 months (i.e. the interval between the initial PET measurements with [11C]raclopride and [18F]MNI-659 and the follow-up PETmeasurement with [18F]MNI-659) will be approximately 14 mSv (approximately 4-5 years of background radiation in Sweden). Although the life expectancy of an HDGEC can be several years or decades, particularly in case of pre-manifest subjects, the risk associated with such a cumulative radiation dose is acceptable, justifying the study in view of the progressive and devastating nature of this fatal disease that currently has no cure or therapy that could halt the progression and modify the disease. There will be no direct benefit to subjects participating in this study. However, this study can provide important information that could be applied to the ongoing development of PDE10 inhibitors in HD and result in an immediate impact on the development of a potential treatment. In addition the results of the longitudinal study could help further understand
PDE10A enzyme involvement in HD and validate PDE10A PET imaging as a suitable biomarker for future clinical trials in HD.
Though PET imaging itself causes no pain there may be some discomfort from having to remain still during the scanning. Claustrophobic subjects may feel some anxiety while being scanned.

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

HDGECs who have participated in and completed study CHDIKI1201/PET-HD-PDE10A .

Exclusion criteria

Any disease, condition, or concomitant medication that significantly compromises the function of the body systems and that in the opinion of the Investigator might interfere with the conduct of the study or its
interpretation. History of other neurological condition (including brain surgery, intracranial haematoma, stroke/cerebrovascular disorders, epilepsy), co-morbidity of psychiatric disorders. History of anaphylactoid or anaphylactic reactions to any allergen including drugs and contrast media.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-11-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]MNI659
Generic name:	2-(2-(3-(1-(2-[18F]fluoroethyl)-1H-indazol-6-yl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-

Ethics review

Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-09-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-002750-39-NL
Other	EudraCT
CCMO	NL54910.058.16