[PETDE10] Imaging of phosphodiesterase 10 A (PDE10A) enzyme levels in the living human brain of Huntington*s disease gene expansion carriers and healthy controls with positron emission tomography

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

Summary

ID

NL-OMON41442

Source
ToetsingOnline

Brief title
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, phosphodiesterase 10 A (PDE10A) enzyme levels, positron emission tomography

Outcome measures

Primary outcome

The primary objective is to measure the availability of the PDE10A enzyme in Huntington*s Disease (HD)gene expansion carriers (HDGECs) by estimating and comparing the distribution volume (VT) of the radioligand [18F]MNI-659 in the striatum (caudate and putamen), globus pallidus, ventral striatum including nucleus accumbens, thalamus, cortex and cerebellum in HDGECs and age (± 5 years)- and gender-matched healthy controls (HCs).

Secondary outcome

The secondary objectives are (as have been described above):

1) To compare the non-displaceable distribution volume (VND) of [18F]MNI-659 in the cerebellum between HDGECs and HCs. If no differences in the VND will be found, the cerebellum will be considered as reference region and the binding potential (BPND) will be estimated as: (VT-VND)/VND and with the simplified reference tissue model SRTM and with the non-invasive Logan graphical analysis.

2) To compare the kinetics, metabolism and the protein binding of the [18F]MNI-659 in HDGECS and HCs.

3) To compare the availability of the PDE10A enzyme in sub-divisions of the striatum (caudate, putamen and ventral striatum including nucleus accumbens) with the D2 receptor availability in the same regions in HDGECs and HCs.
4) To explore the correlation between the availability of the PDE10A enzyme (VT or BPND) and the number of CAG repeats in HDGECs.
5) To explore the correlation between the availability of the PDE10A enzyme (VT or BPND) in HDGECs and disease duration (the classical definition of time when motor clinical manifestation first became noticeable will be used), clinical ratings (stage and Unified Huntington*s Disease Rating Scale [UHDRS]), functional assessments (Total Motor Score [TMS] and Total Functional Capacity [TFC]) and psychiatric and cognitive assessments (Cognitive Battery Assessment [CBA]).

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 hallmark of the disease is the accumulation of aggregates of mutated huntingtin, which has been found to impair cyclic adenosine monophosphate (cAMP) signaling and gene transcription mediated by the cAMP responsive-element binding protein (CREB). Phosphodiesterase 10 A (PDE10A) is an enzyme which is highly enriched in the mediumsized spiny neurons of the striatum and has an important role in the regulation of cAMP and cyclic guanosine monophosphate (cGMP) levels. Targets genes of CREB include those responsible for neurotransmitter synthesis, release and signaling 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 signaling.
Preliminary data in human subjects suggest that [18F]MNI-659 is a suitable

radioligand for imaging PDE10A in vivo.

Study objective

The primary objective is to measure the availability of the PDE10A enzyme in Huntington*s Disease (HD)gene expansion carriers (HDGECs) by estimating and comparing the distribution volume (VT) of the radioligand [18F]MNI-659 in the striatum (caudate and putamen), globus pallidus, ventral striatum including nucleus accumbens, thalamus, cortex and cerebellum in HDGECs and age (± 5 years)- and gender-matched healthy controls (HCs).
The secondary objectives are:
1) To compare the non-displaceable distribution volume (VND) of [18F]MNI-659 in the cerebellum between HDGECs and HCs. If no differences in the VND will be found, the cerebellum will be considered as reference region and the binding potential (BPND) will be estimated as: (VT-VND)/VND and with the simplified reference tissue model SRTM and with the non-invasive Logan graphical analysis.
2) To compare the kinetics, metabolism and the protein binding of the [18F]MNI-659 in HDGECS and HCs.
3) To compare the availability of the PDE10A enzyme in sub-divisions of the striatum (caudate, putamen and ventral striatum including nucleus accumbens) with the D2 receptor availability in the same regions in HDGECs and HCs.
4) To explore the correlation between the availability of the PDE10A enzyme (VT or BPND) and the number of CAG repeats in HDGECs.
5) To explore the correlation between the availability of the PDE10A enzyme (VT or BPND) in HDGECs and disease duration (the classical definition of time when motor clinical manifestation first became noticeable will be used), clinical ratings (stage and Unified Huntington*s Disease Rating Scale [UHDRS]), functional assessments (Total Motor Score [TMS] and Total Functional Capacity [TFC]) and psychiatric and cognitive assessments (Cognitive Battery Assessment [CBA]).

Study design

The aim of this study is to measure the availability of the PDE10A enzyme in HDGECS using the recently developed radioligand [18F]MNI-659. The study will be cross-sectional, examining HDGECs at different stages of the disease (pre-manifest, stage 1 and stage 2), in comparison with HCs, matched by age and gender. The HDGECs included in this study will be recruited from the large database of the REGISTRY or ENROLL-HD studies. The study will have an adaptive design, consisting of the following steps:
1a) Inclusion of 4 HCs in the first cohort to confirm quantification, metabolism, and protein binding of [18F]MNI-659. These 4 HCs will be recruited based on the demographics (age and gender) provided by European Huntington-Disease Network (EHDN) for the first cohort of stage 1 HDGECs to be included.
1b) Inclusion of 5 stage 1 HDGECs and 1 additional HC (matched by age and

gender) in the first cohort to measure the availability of the PDE10A enzyme.
2) Inclusion of approximately 10 HDGECs and an equal number of HCs (matched by age and gender) in the second cohort. The HDGECs will be either:
a) Pre-manifest HDGECs, if PDE10A levels (VT) are decreased by more than 40% in the first cohort of stage 1 HDGECS.
b) Additional stage 1 HDGECS, if PDE10A levels (VT) are decreased by between 30 and 40% in the first cohort of stage 1 HDGECs. In addition, approximately 5 additional stage 2 HDGECs may be recruited within this cohort or
c) Stage 2 HDGECs, if PDE10A levels (VT) are decreased by less than 30% in the first cohort of stage 1 HDGECs.
3) Inclusion of additional HDGECs and HCs (matched by age and gender) to provide further sample size to explore the correlation between PDE10A level (VT or BPND) and clinical measures and between PDE10A levels (VT) and CAG repeats.

In the study, comprising all steps, there will be approximately 45 HDGECs and an equal number of HCs.

The HDGECS will perform 5 study visits (screening, screening telephone follow-up, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and telephone follow-up) during a maximum of 97 days.
The healthy controls will perform 4 study visits (screening, MRI, PET and telephone follow-up) during a maximum of 97 days.

Interim data analyses will be performed after steps 1a, 1b and 2 and the results will be evaluated by an Interim Review Committee (ICR). The committee will decide whether to continue or stop the study and will also decide the additional number of HDGECs of each HD stage to be included in the study.

Study burden and risks

The radioligands [11C]raclopride and [18F]MNI-659 will be administered at doses less than 10 micrograms, within the micro dosing concept, and no pharmacological effects are expected. [11C]raclopride is a well-established radioligand for the dopamine D2 receptors that was developed at the Karolinska Institute (KI) in the 1980s and is the PET radioligand most widely used worldwide. No safety issues have ever been reported. [18F]MNI-659 has been administered to 9 healthy volunteers at the Molecular Neuroimaging Center, New Haven, CT, USA, without any safety concern.
The injected radioactivity of [11C]raclopride will be 300 MBq/70 kg of body weight ±10% and of [18F]MNI-659 it will be 185 MBq/70 kg of body weight ±10%. The effective dose for the injection of [11C]Raclopride + [18F]MNI-659 is 8 mSv (2 years of background radiation in Stockholm).
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.
Arterial blood sampling will be performed for the PET measurements done with

[18F]MNI-659 to derive the input function for the compartmental analysis. A total of approximately 110 mL blood will be drawn. Arterial cannulation will be performed by a neuro-anaesthesiolgist under local anaesthesia. Arterial cannulation can be associated with a formation of a haematoma. To prevent or reduce haematoma, a local compression for approximately 20 min will be made on the site of cannulation at the end of the PET measurements.
No specific benefits for the HCs in the current study are foreseen except for the medical screening. Subject remuneration will be paid to each participating HC after study completion. The remuneration covers loss of time and any inconvenience caused by study participation.
The HDGECs will be compensated for their travel expenses. They will receive no immediate benefit from participating in the study, the only potential benefit is a better understanding of HD and the possibility that the information obtained in this study will lead to potential treatments in the future.

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

- Age 18 to 70 years, inclusive;- (HCs): Healthy according to medical history, physical examination, ECG, vital signs, laboratory assessment and MRI, with a body mass index between 19 and 27 (both inclusive);- HDGECs: Otherwise healthy according to medical history, no comorbidity of psychotic disorders, physical examination, vital signs and laboratory assessments, and with a body mass index (BMI) between 19 and 27 (both inclusive)
- (HDGECs): (A) HD Stage 1 or HD Stage 2: Patients with a clinical diagnosis of HD, defined by the presence of noticeable motor disorder and *36 CAG repeats (HD stage 1: TFC 11-13, HD stage 2: TFC 7-10); (B) Pre-manifest: Subjects that are carriers of the mutant Huntington gene with *40 CAG repeats, a Total Motor Score *5 and disease burden score of either * 250 (early pre-manifest) or a disease burden score * 275 (late pre-manifest); disease burden score is calculated with the equationa ((CAGn-35.5) X age))

Exclusion criteria

- HDGECs and HCs: 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 anaphylactoid or anaphylactic reactions to any allergen including drugs and contrast media.;- Contraindication to MRI, such as known claustrophobia, presence of metal devises or implants (e.g. pacemaker, vascular- or heart- valves, stents, clips), metal deposited in the body (e.g. bullets or shells), or metal grains in the eyes.;- HDGECs: History of other neurological condition (including brain surgery, intracranial haematoma, stroke/cerebrovascular disorders, epilepsy), co-morbidity of psychotic disorders.;- HCs: Family history of HD.

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):	07-06-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]MNI-659
Generic name:	2-(2-(3-(4-(2-[18F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropox
Product type:	Medicine
Brand name:	RACLOPRIDE([11C]METHOXY)
Generic name:	3,5-dichloro-N-{[(2S)-1-ethylpyrrolidin-2-yl]methyl}-2-hydroxy-6-methoxybenzamide

Ethics review

Approved WMO Date:	30-01-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-03-2014

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-08-2015
Application type:	Amendment
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	EUCTR2012-003808-13-NL
CCMO	NL42130.058.12