The Dutch Parkinson-GBA Cohort Study (DUPARG)
Cognitive and cholinergic function analysis in Dutch Parkinson*s patients with GBA variations.

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The primary objective of this study is to compare cholinergic innervation of the cerebral cortex of GBA-PD and non-GBA-PD patients, using [18]FEOBV PET imaging of the brain.

Ethical review	Approved WMO
Status	Completed
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON50798

Source
ToetsingOnline

Brief title
The Dutch Parkinson-GBA Cohort Study

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Michael J Fox foundation

Intervention

Keyword: acetylcholine, GBA variations, Parkinson's disease, PET imaging

Outcome measures

Primary outcome

The primary endpoint is the regional VAChT binding, as a measure of brain cholinergic innervation, measured with FEOBV PET imaging.

Secondary outcome

Secondary endpoints include (1) Neuropsychological assessment (NPA) covering all cognitive domains including questionnaires, (2) GCase activity measured using a flow cytometry based assay of peripheral blood mononuclear cells (PBMCs), (3) [18F]DOPA PET to evaluate the dopaminergic system, (4) Magnetic Resonance Imaging (MRI) and, (5) relevant clinical characteristics of the patients.

Study description

Background summary

Parkinson's disease (PD) is a multifactorial disorder, with both environmental and genetic risk factors playing important roles in its etiology and progression. The most common genetic risk factor for PD involve mutation of the GBA1 (GBA) gene, encoding the lysosomal enzyme glucocerebrosidase (GCase). Approximately, 15% of Dutch PD patients has one or more GBA mutation. PD patients who carry GBA mutations putatively comprise a distinct clinical subtype, with a younger age at onset and faster progression of the disease. GBA-PD is associated with more severe cognitive impairment, mood disorders,

postural instability and gait disorders (PIGD) and hyposmia. The GBA-PD phenotype bears similarity with cholinergic system degeneration symptomatology, which is an important but variable feature of PD, in particular the cognitive impairment and postural instability and gait disorders (PIGD). Here, we will explore using PET-imaging techniques if GBA mutations lead to preferential degeneration of the cholinergic system. Additionally, the contribution of reduced Case activity to the clinical status of PD subjects will be assessed.

Study objective

The primary objective of this study is to compare cholinergic innervation of the cerebral cortex of GBA-PD and non-GBA-PD patients, using [18]FEOBV PET imaging of the brain.

Study design

We propose a cross-sectional study design, to compare cholinergic innervation of GBA-PD - with non-GBA-PD patients.
The proposed study will include PD subjects with a known GBA mutation. These GBA-PD subjects stem from two already existing study cohorts and by creating a new GBA-PD cohort The first cohort contains of a Dutch national cohort of >500 GBA-PD patients, identified through a nation-wide screening in the Netherlands (GBA-NLD) (Den Heijer et al, 2020)(1).. Participants from the Dutch Parkinson Cohort (DUPARC) [METc 2017/142; NL60540.042.17]: a longitudinal cohort study of 150 de novo PD subjects will be enrolled. The measurements to perform in this study are already approved by the METc for the DUPARC participants and permission had been given by the patients to use their research data. Additional participants will be recruited by cooperation of a collaborative network of PD treating neurologist in the northern part of the Netherlands (Parkinson Platform Northern Netherlands, PPNN). Patients treated by neurologist of the PPNN will be informed about the study. Patients will be asked to collect a saliva sample to analyse the GBA carrier status. Patients with a GBA mutation who meet the in- and exclusion criteria are asked to participate in the study after giving informed consent. Also specified subjects with L444P GBA carrier status and E326K GBA carrier status will be enrolled to compare the cholinergic innervation and cognitive functioning between these mild and severe GBA variants, based on the clinical data so far.
The GBA-NLD subjects and additional subjects enrolled through the PPNN receive measurements in concordance with the DUPARC protocol. Patients will undergo the following measurements and questionnaires: Demographics, detailed medical history, extensive neuropsychological assessment (NPA), GCase activity using peripheral mononuclear blood cells (PBMCs) and imaging including FEOBV PET, F-DOPA, MRI brain. METc persmission has already been granted to perform the measurements on the DUPARC participants and permission had been given by the patients to use their research data. This METc application asking permission to perform the measurement for the GBA-NLD participants and participants enrolled

through the PPNN.

Study burden and risks

Participants from the GBA-NLD study and the participants enrolled through the PPNN will undergo additional questionnaires and assessments. Those patients will receive measurements in concordance with the DUPARC three-year follow-up protocol.
This will include: FEOBV PET, FDOPA PET and a MRI. In addition, 60ml of blood for the assessment of Gcase activity, neuropsychological assessment (NPA), and motor assessments (UPDRS). The total examination will take two full-day visits to the UMCG.
The radiation burden of the FEOBV-PET is 4,6mSv (with 200 MBq injection). For attenuation correction a low-dose CT is also added to each PET scan performed. This accounts for an addition radiation burden of 1,5 mSv.
To provide insight in the presynaptic dopaminergic integrity and related disease activity, F-DOPA PET scans will be performed. The radiation burden of the F-DOPA PET scan is 5,2 mSV (with 200 MBq injection) and an added 1,5 mSv low-dose CT for attenuation correction. In total, the radiation burden of both scans will be 12,8 mSv. There are no benefits associated for the participants with participation.
Contrary to previous research, the current proposal provides the unique opportunity for in-depth phenotyping of large numbers of GBA-PD subjects in a homogenous, single-center, study protocol. In itself, thorough phenotyping will provide health care professionals with reliable data to offer useful prognostic information and personalized treatment, in particular regarding cognitive deterioration, a major concern amongst PD subjects. Besides more solid data of the clinical subtype of GBA-PD, this will also be the first study to use various imaging parameters of GBA-PD, including cholinergic PET imaging using FEOBV. As the clinical manifestation of GBA-PD suggest cholinergic involvement, FEOBV-PET imaging will provide valuable insights in the neuro-anatomical structures underlying the GBA-PD subtype. Moreover, it can inform treatment decisions concerning cholinergic supplementation in both GBA-PD and non GBA-PD subjects with cognitive impairments.
The clinical spectrum of GBA-PD seems less heterogeneous compared to non GBA-PD with faster clinical progression, making GBA-PD interesting subtype for disease-modifying trials, in particular aimed at increasing GCase activity. Stratification according to GBA status might therefore reduce the sample sizes and follow-up required for well-powered clinical trials. Besides GBA status, the current proposal also allows for stratification according to biomarker profiles, including GCase activity and brain cholinergic innervation, that are putatively relevant for both GBA-PD and non GBA-PD.

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

- Diagnosis Parkinson*s disease according to UK Parkinson's Disease Society Brain Bank criteria
- Willingness to cooperate and sign written informed consent

Exclusion criteria

- The refusal to be informed about an unforeseen clinical finding, Exclusion from PET: - pregnant or breast feeding women, Exclusion from MRI scan: - MRI incompatible implants in the body (e.g. prothesis, pacemakers, implanted heart valves.) - Any risk of having metal particles in the eyes due to manual work without proper eye protections - Tattoos containing red pigments that form a

safety risk

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-06-2021
Enrollment:	205
Type:	Actual

Ethics review

Approved WMO Date:	15-03-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL75764.042.20