Aromatic L-amino acid decarboxylase activity, tyrosine decarboxylase activity and gut microbiome in patients with advanced Parkinson*s disease

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Primary Objective: Determining the prevalence in advanced-stage PD patients of increased bacterial TDC activity in faeces and the prevalence of increased AADC activity in serum.Secondary Objectives:- Correlating TDC activity and AADC activity to...

Ethical review	Approved WMO
Status	Completed
Health condition type	Malabsorption conditions
Study type	Observational invasive

Summary

ID

NL-OMON51457

Source
ToetsingOnline

Brief title
AADC/TDC in advanced Parkinson*s disease

Condition

- Malabsorption conditions
- Movement disorders (incl parkinsonism)

Synonym
idiopathic parkinsonism, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Maag Lever Darm Stichting;ParkinsonNL;Stichting Alkemade-Keuls;Stichting Woelse Waard

Intervention

Keyword: AADC, Levodopa, Parkinson, TDC

Outcome measures

Primary outcome

Prevalence of increased TDC activity in faeces and increased AADC activity in serum.

Secondary outcome

Correlation of TDC activity in faeces / AADC activity in serum to:

- Treatment response, which is defined as the magnitude of the difference between the MDS-UPDRS part III score in the ON state versus the practically-defined OFF state (ΔOFF-ON)

- MDS-UPDRS part III (baseline score)

- MDS-UPDRS part IV (single moment of measurement)

- TUG (baseline score and ΔOFF-ON)

- Purdue Pegboard Test (baseline score and ΔON-OFF)

- Composite Clinical Motor Score, which is a composite of MDS-UPDRS-III, TUG and pegboard test scores (baseline score and ΔOFF-ON)

- modified Hoehn & Yahr score (baseline score and ΔON-OFF)

- subjective clinimetrics scores (WOQ-9, SIBO questionnaire, Schwab&England scale, self-reported medication effect)

- medication use (levodopa equivalent dose (LED), dosage frequency, use of

non-levodopa dopaminergic medication, total duration of use of PD medication)

- duration of disease (time since diagnosis)

- comorbidities

- diet

Correlation of abundance of TDC-producing bacteria in faeces to:

- TDC activity in faeces;

- the dependent variables described above;

- factors associated with socioeconomic status (ethnicity, type of dwelling,

paid work, main daily activity, highest completed education, total number of

years of education).

Correlating factors associated with socioeconomic status to treatment response.

Study description

Background summary

Many persons with Parkinson*s disease (PD), estimated at 20% in our centre, develop a progressive resistance to levodopa, which is the pharmacological mainstay of PD treatment. These persons gradually lose responsiveness to levodopa and develop an aberrant response with delayed effect and unpredictable fluctuations. Recently, two enzymatic pathways have been identified that could be (partially) responsible for this:
1) breakdown of levodopa by bacterial tyrosine decarboxylase (TDC), an enzyme which normally decarboxylates dietary tyrosine but which is also able to decarboxylate levodopa. Compared to normal subjects, PD patients are prone to alterations in gut microbiota, including an increased abundance of Akkermansia, Lactobacillus and Bifidobacterium and a decreased abundance of Prevotella. Of these, Lactobacillus brevis is a TDC-producing species. Additionally, accumulation of bacterial TDC in the small intestine may occur in the context of small-intestinal bacterial overgrowth (SIBO) for which persons with PD have

an increased risk and which has been reported to be present in 46% of PD patients. Bacterial TDC has the potential to prematurely metabolize levodopa, hence limiting its bioavailability and effect.
2) paradoxical induction of activity of the enzyme aromatic L-amino acid decarboxylase (AADC) in chronic users of levodopa combined with a peripheral decarboxylase inhibitor (PDI). This enzyme normally converts levodopa to dopamine, which is unable to cross the blood-brain barrier. Therefore, in a therapeutic setting levodopa is combined with a PDI which inhibits AADC peripherally, greatly increasing the bioavailability of levodopa to the brain. It has, however, been found that chronic use of levodopa/PDI can lead to a paradoxical induction of AADC activity, leading to a premature breakdown of levodopa and limitation of its bioavailability and effect.

Studies examining a possible relationship between TDC and AADC activity on one hand, and clinical characteristics of PD patients on the other, have thus far been small and/or examined few variables. In a separate study, we will be using the large (n=520) Personalized Parkinson Project (PPP) cohort to examine this relationship. However, the PPP cohort consists entirely of persons in whom the PD diagnosis is fairly recent (up to 5 years before inclusion). Levodopa resistance is more likely to develop later in the disease course. Therefore, a sample of patients with more advanced PD is needed.

As detailed above, it has been well-described that persons with PD have a different composition of the intestinal microbiome as compared to healthy individuals. Indeed, an altered gut microbiome might be a prerequisite for the development of PD. More recently, indications have been found that within PD patients, the microbiome differs between patients with and without motor complications (possibly related to bacterial TDC production, as described above). A possible risk factor for an altered gut microbiome appears to be socioeconomic status. Given the above, this may influence the risk of developing PD and/or the risk of developing motor complications of PD.
Data and biospecimen samples from this cross-sectional study can be used to further explore the relationship between gut microbiome composition on the one hand, and TDC activity, motor complications and socioeconomic status on the other.

Study objective

Primary Objective: Determining the prevalence in advanced-stage PD patients of increased bacterial TDC activity in faeces and the prevalence of increased AADC activity in serum.
Secondary Objectives:
- Correlating TDC activity and AADC activity to clinical parameters;
- Correlating abundance of TDC-producing bacteria in advanced-stage PD patients to bacterial TDC activity;
- Correlating abundance of TDC-producing bacteria in advanced-stage PD patients to clinical markers associated with levodopa unresponsiveness / motor

complications;
- Correlating abundance of TDC-producing bacteria in advanced-stage PD patients to socio-economic status, and by extension, correlating socio-economic status to response fluctuations.

Study design

Cross-sectional, observational with invasive measurements.

Study burden and risks

Although in a separate study, we will investigate AADC and TDC enzyme activity and their clinical correlates in already-collected data and biosamples, those were collected in patients with a recent PD diagnosis. There are indications that increased enzyme activity, and related levodopa resistance, are more likely to occur in patients with more advanced PD. A new study is therefore necessary to examine this, in order to obtain a better external validity for the PD population as a whole. The risks associated with this study are deemed to be negligible. There are no specific benefits for the subjects associated with participation in this study. As unintended advantages, OFF/ON-scoring may provide subjects with more insight into the effect levodopa has on their symptoms, and the results of their enzyme assays (if they would request these to be shared with them) may provide subjects with insight into a reason for their levodopa (un)responsiveness. Also, for external participants in whom there is uncertainty over the correctness of the diagnosis, the screening visit may provide them with more diagnostic certainty.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Subject has Parkinson*s disease of at least 5 years duration, defined as time since diagnosis made by a neurologist;
- Subject is an adult, at least 25 years of age;
- Subject can read and understand Dutch;
- Subject has completed the METC-approved Informed Consent;
- Subject is willing, competent, and able to comply with all aspects of the protocol,
including not taking their PD medication during a 12-hour period, and biospecimen collection.

Exclusion criteria

- Co-morbidities that would hamper interpretation of parkinsonian disability, such as coincident musculoskeletal abnormalities, as judged by the investigators;
- Significant doubt over the correctness of the diagnosis PD, as judged by the investigators;
- Not able to stand or walk without the assistance of another person (walking aids are not an exclusion criterion);
- Never having used levodopa;
- No current use of levodopa due to lack of effect, despite never having used at least 600mg/day during at least 1 month;
- Documented allergy or contraindication to either levodopa or benserazide;
- Documented severe and debilitating dyskinesias on levodopa, to such an extent that levodopa treatment was terminated;
- Current pregnancy or breastfeeding;
- Co-morbidity with primary gastrointestinal pathology associated with altered gut microbiota and/or altered absorption (such as inflammatory bowel disease,

celiac disease, colorectal carcinoma);
- Antibiotic use at any time during the 12 months leading up to the clinic visit;
- Current or recent (less than 1 month before clinic visit) use of (non-parkinson) drugs known or suspected to influence AADC activity, including amphetamine, dexamethasone, dopamine receptor antagonists, monoamine oxidase (MAO) inhibitors (including MAO-B inhibitors which are infrequently used as antiparkinsonian drugs), prostaglandin E2, and vigabatrin.

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):	24-07-2023
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	19-12-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT05558787
CCMO	NL82727.091.22