Cognitive-driven ADL impairment as a predictor for Parkinson's disease dementia (PDD)

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2. List of abbreviations

ABC-PD	Amyloid-Beta in Cerebrospinal Fluid as a Risk Factor for Cognitive Dysfunction in Parkinson's Disease
AD	Alzheimer's Disease
ADL	Activities of Daily Living
CERAD	Consortium to Establish a Registry of Alzheimer's Disease
CSF	Cerebrospinal Fluid
FAQ	Pfeffer Functional Activities Questionnaire
IQ-CODE	The Informant Questionnaire on Cognitive Decline in the Elderly
LPS 50+	Leistungsprüfsystem für 50- bis 90-Jährige
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PD-CN	Parkinson's Disease with Normal Cognition
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PIB	Pittsburgh Compound B, detects parenchymal Amyloid-beta
RBD	REM(Rapid Eye Movement) Behavior Disorder
UKT	Universitätsklinikum Tübingen
UPDRS	Unified Parkinson‘s Disease Rating Scale
WIE	Wechsler Intelligenztest für Erwachsene

3. Study summary

3.1. Background

Presence and severity of non-motor symptoms modulates the rate of Parkinson's Disease (PD) progression with a high impact on patients' quality of life [1-3]. One major clinical milestone in the course of the disease is the conversion to Parkinson's disease dementia (PDD), dramatically increasing the risk for nursing home placement and mortality [4]. One of the greatest risk factors for PDD is the development of mild cognitive impairment in PD (PD-MCI) [5]. However, only a subgroup (26% to 39.1%) of patients with PD-MCI have been reported to convert to dementia, while others present with a stable cognitive status or revert to normal cognitive function [6-8]. For an early and effective treatment, the identification of a high-risk group for PDD among those with PD-MCI is essential.

The core feature that differentiates PDD from PD-MCI is the loss of the ability to perform activities that are necessary for independent living [9, 10], emphasizing the importance of valid and reliable activities of daily living (ADL) assessments in PD [11]. To confirm the diagnosis of PDD, ADL disabilities should be primarily caused by cognitive, not motor, dysfunction [10, 12]. As PD is primarily a movement disorder, the distinction between motor and non-motor contributions to ADL in PD is an obvious challenge [13].

ADL can be divided into basic (e.g. self-maintenance skills) and instrumental functions (e.g. complex skills). Of these, instrumental ADL function is impaired in the earlier stages whereas basic ADL can be preserved for a long time [14]. In Alzheimer's disease (AD), the combination of slight ADL impairment and mild cognitive impairment increases the risk for dementia, as opposed to the presence of only one of these characteristics [15, 16]. In PD, there is also evidence to assume that mild ADL impairments in PD-MCI characterize those patients at high risk for PDD, as mild signs of ADL impairment are observed in a subgroup of PD-MCI patients as a potential prodromal sign for PDD [14, 17-20]. So far, only a few studies have focused on the interaction between cognitive performance and ADL function in PD. First reports indicate that the cognitive profile of those PD-MCI patients with and without mild signs of ADL impairment does not differ [18, 21]. This implicates that (i.) neuropsychological tests lack predictive value for PDD [22, 23], (ii.) the ADL instruments used might not be suitable to detect cognitive-driven ADL impairment as they cover the characteristic motor signs of PD, or (iii.) sample sizes of previous studies were too small to reveal a between-group effect. Therefore, an economic and valid ADL measure for cognitive decline is needed to evaluate the prognostic value of mild ADL impairment for PDD conversion. We propose the follow-up of an already existing large, non-demented baseline PD cohort to longitudinally investigate the association between ADL function and cognitive performance along with blood and cerebrospinal Fluid (CSF) biomarker profiles.

3.2. Preliminary data

Methods. In a cohort of 216 non-demented PD patients (41.2%, with PD-MCI), assessed within the frame of the ongoing "Amyloid-Beta in Cerebrospinal Fluid as a Risk Factor for Cognitive Dysfunction in Parkinson's Disease" (ABC-PD) study, we developed a novel quotient score from the Pfeffer Functional Activities Questionnaire (FAQ) [24]. The FAQ is a 10 item instrumental ADL assessment scored on a 4-point Likert scale ranging from normal (score=0) to dependent (score=3) ADL function (max. points 30) [25].

The novel FAQ quotient was developed by differentiating cognitive and motor aspects of the individual items. Ten linear regressions were conducted defining each FAQ item as the dependent variable, and the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III), motor assessment) as well as the Montreal Cognitive Assessment (MoCA) total score as independent variables, with age, sex, and disease duration entered as covariates.

Results Part 1: Construction of FAQ-Quotient. As a result, the items 1-(accounting for finances), 2-(tax/business records) and 9-(remembering important events) showed associations with the MoCA score, whereas the items 3-(shopping alone), 4-(skills & hobbies), 5-(using appliances), 6-(meal preparation), 10-(traveling out of house) were found to be significantly associated only with the UPDRS-III score. Item 7-(current events) and 8-(information intake) were associated with both motor and cognitive function and were therefore included into both scores as a constant. Based on the regression analyses, the set of items for cognitive function was defined as, S_{cog} = {1,2,7,8,9} while the set of items reflecting motor function was defined as S_{mot} = {3,4,5,6,7,8,10}. If S_i denotes the score obtained in item *i* for a patient and $S_{i,max}$ denotes the maximum score possible for item *i*, then the following subscores were defined as:

$$FAQ_C = \sum_{i \in S_{cog}} \frac{s_i}{s_{i,max}} \qquad FAQ_M = \sum_{i \in S_{mot}} \frac{s_i}{s_{i,max}} \qquad FAQ_Q = \frac{FAQ_C + 1}{FAQ_M + 1}$$

FAQ_Q: The quotient was formed by dividing the cognitive aspect (FAQ_C) by the motoric aspect (FAQ_M); a value >1 ($FAQ_{Q>1}$) indicates more cognitive- compared to motor-related ADL impairment.

Results Part 2: Validation of FAQ-Quotient. Out of the 89 PD-MCI patients, 32.6% presented with FAQ_Q values >1, while 67.4% had an FAQ_Q ≤1. The frequency of males was comparable between both PD-MCI subgroups ($FAQ_{Q>1}$ 65.5%, $FAQ_{Q\leq1}$ 63.3%; p=0.99). Logistic regression analyses showed that patients defined as PD-MCI $FAQ_{Q>1}$ were more impaired in tests assessing attention/working memory (p=0.033) and language performance (p = 0.019) than the PD-MCI $FAQ_{Q\leq1}$ group, while motor symptom severity revealed no significant difference between groups (p=0.095). Therefore, subgrouping PD-MCI patients according to the cognitive and motor performance in the FAQ is suitable for differentiating between different levels of severity for cognitive impairment in PD.

4. Objectives of the study

The FAQ is an economic and easy to apply ADL scale. Items of the FAQ have been previously published [25, 26]; details of the construction of our FAQ parameters are currently under review for publication and will also be available without additional costs.

The aim of our project is to evaluate whether the combination of PD-MCI along with cognitive-driven ADL impairment predicts the future development of PDD and might be able to differentiate between those PD-MCI patients with a high risk for the development of PDD from those with stable PD-MCI. The identification of a high-risk group for PDD among those with PD-MCI is essential for upcoming clinical trials targeting cognitive impairment in its earliest stages.

4.1. Hypothesis and research questions

Based on previous reports and preliminary results, we hypothesize that PD-MCI patients with a more pronounced cognitive-driven ADL impairment ($FAQ_{Q>1}$) are at higher risk for conversion to PDD than PD-MCI patients with ADL impairment primarily related to motor function ($FAQ_{Q\leq1}$).

1. Stratification of subgroups according to their baseline cognitive status (PD-MCI vs. normal cognition, PD-CN) and ADL function (cognitive-driven ($FAQ_{Q>1}$) vs. motor-driven ($FAQ_{Q\leq1}$)).
2. Defining progression of ADL impairment over time.
   Aim 2.1: Evaluation of stability and/or progression of ADL status between baseline and follow-up ($FAQ_{Q>1}$ vs. $FAQ_{Q\leq1}$).
3. Evaluation of the interaction between cognition and ADL function over time.
   Aim 3.1: Evaluation of conversion rates to PD-MCI and PDD according to baseline ADL status ($FAQ_{Q>1}$ vs. $FAQ_{Q\leq1}$).
   Aim 3.2: Prediction of PD-MCI (among PD-CN) and PDD according to baseline ADL, cognitive, genetic, and biomarker profiles in blood and CSF.
   Aim 3.3: Progression of decline in cognition and ADL function in relation to Amyloid and Tau burden.

5. Study duration

Total duration of the study is 2 ½ years.

6. Study population

6.1. Study population

Between March 30th, 2014 and December 31th, 2017, we recruited a large cohort of 262 PD patients within the frame of the Amyloid-Beta in cerebrospinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease" (ABC-PD, ethic protocol 686/2013B01) study. Of the total baseline sample, 43% were diagnosed with PD-MCI (63% males, mean age of 67.2±7.7 years) whereas 57% had normal cognitive function (61% males, mean age of 65.4±8.7 years). Mean disease duration of the total sample was 5.1±3.9 years.
We propose to follow-up the already existing ABC-PD cohort described above with a longitudinal assessment including neuropsychological in-depth endophenotyping and CSF biomarker analyses. The estimated mean follow-up interval is 46.6±6.6 months.

6.2. In- and exclusion criteria for follow-up assessment

The investigator will ensure that all patients considered for the study meet the inclusion and exclusion criteria described in Sections 6.2.1 and 6.2.2.

6.2.1. Inclusion criteria

- 50 –90 years of age.
- Diagnosis of PD according to the United Kingdom Brain-Bank criteria.

- Ability to communicate well with the investigator, to understand and comply with the requirements of the study.
- Provide written informed consent to participate in the study and understand their right to withdraw consent at any time without prejudice to future medical care.

6.2.2. Exclusion criteria

- Any disability that may prevent the subject from completing the informed consent form or other study requirements.
- Other neurodegenerative disease which renders the subject unable to communicate well with the investigator or to understand and comply with the requirements of the study.
- Participation in any clinical investigation of a new investigational compound or therapy within 4 weeks prior to baseline visit, and for any other limitation of participation based on local regulations.
- Alcohol, medication or drug dependency or abuse (except for nicotine).
- History of brain disease other than PD, e.g. head trauma, stroke, encephalitis, etc.

6.3. Recruitment

Participants of the already recruited ABC-PD cross-sectional cohort (ethic protocol 686/2013B01) will be asked to participate in the follow-up assessment. Patients who did not agree to participate in a longitudinal study or who have asked not to be contacted after the first cross-sectional assessment will not be contacted again. A drop-out rate of 20% is expected for follow-up retention. Therefore, investigation of 209 patients will be conducted between August 2018 and April 2020. During the executive project phase, three patients will be assessed weekly (~12 per month). Patients will be contacted either via phone or in written form. Reason for drop-outs will be registered for data analysis.

7. Statistics and Sample size estimation

The relative risk as well as the positive and negative Likelihood Ratios according to baseline group status for conversion to PD-MCI or PDD will be calculated.

1. Between-group differences will be conducted using either a Student's t-test, analyses of variance (ANOVA), or covariance analyses.
2. For longitudinal within-group analyses of cognitive and ADL progression, we will use either paired t-tests or repeated ANOVA models. Additionally, Kaplan Mayer survival curves and Cox proportional hazard models stratified by the individual group status (e.g. PD-MCI with and without cognitive-driven ADL impairment) will be applied to estimate the time period to PD-MCI or PDD conversion.
3. Associations between serum and CSF markers along with ADL and cognitive data will be carried out using multivariate regression analyses in order to evaluate the type of biomarker that best reflects the biological impact on phenotype and progression.

Reports on conversion rates of new-onset PD-MCI and PDD are highly variable between studies [5]. At a mean follow-up interval of around four years, the frequency of PDD in large

PD cohorts is estimated to vary between 13% [7] and 28% [27], resulting in 27 to 58 patients with PDD in the present cohort at follow-up. New-onset PD-MCI is expected to be higher, with around 49 (36%) [6] to 107 (78%) cases in our cohort [27]. Of all PD-MCI patients, one-third are classified as having cognitive-driven compared to motor-driven ADL impairment, resulting in at least 16 to 35 new-onset PD-MCI patients classified as $FAQ_{Q>1}$ [24]. These estimates resemble the sample size of our preliminary data described above, for which between-group differences have been statistically verified. Therefore, we conclude that moderate to strong effects can be detected with 80% power in two-group comparisons.

8. Assessments

Table 1: Overview of assessments

Assessment of PD patients	Time
Explanation of the study requirements	10 min
Demographics & lifestyle	
Age, gender, education, occupation, family history of neurodegenerative diseases, smoking/drinking behavior, height & weight	5 min
Neurological Assessments:	
Medication intake, concomitant diseases, and procedures	10 min
Unified Parkinson's Disease Rating Scale (UPDRS) Parts III-IV, Hoehn & Yahr Stage	15 min
Olfactory testing using the Sniffin Sticks 12 odor test	3 min
PD Non-Motor Symptom Scale, subscales 1-5 (PD-NMS-S)	5 min
Unified Multiple System Atrophy Rating Scale (UMSARS) I: History of autonomic symptoms	2 min
Cognitive test battery:	
History and self-awareness of cognitive deficits	5 min
Montreal Cognition Assessment (MoCA)	10 min
Mini Mental State Examination (MMSE)	5 min
Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus, German Version)	25 min
Trail Making Test Parts A and B	10 min
Fragmented Words (Subtest of the Leistungsprüfsystem für 50- bis 90-Jährige, LPS 50+)	5 min
Digit-Symbol Test (Subtest of the Wechsler Intelligenztest für Erwachsene, WIE)	5 min
Similarities (Subtest of the WIE)	5 min
Letter-Number Sequencing (Subtest of the WIE)	5 min
Demenz Apraxie Test (DAT)	5 min
Pill-Questionnaire	5 min
Patient Questionnaires (can be filled out at home):	
Parkinson's Disease-Non-motor Symptoms Questionnaire (PD-NMS-Q)	3 min
Beck Depression Inventory – II (BDI-II)	5 min
Geriatric Depression Scale (GDS)	2 min
Beck-Anxiety-Inventory (BAI)	2 min
Functional Activities Questionnaire (FAQ)	2 min
Parkinson's Disease Activities of Daily Living Scale	1 min
Parkinson's disease Questionnaire (PDQ-39)	5 min
Freezing of Gait Questionnaire (FOG)	1 min
Epworth Sleepiness Scale (ESS)	2 min
REM Sleep behavior questionnaire (RBDS-Q)	2 min
Apathy Evaluation Scale (AES)	3 min
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Short (QUIP-Kurz)	3 min
Unified Parkinson's Disease Rating Scale (UPDRS) Parts I-II	6 min
International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF)	2 min
Patient Perception of Bladder Condition (PPBC)	1 min
Top-10 Priority List	5 min
Saarbrücker Persönlichkeitsfragebogen (SPF)/ Interpersonal Reactivity Index (IRI)	5 min
Total time of clinical assessment:	**185 min**
Optional Home-based movement assessment (Accelerometer)	**7 days**

For this scientific study, all investigations will be performed in an ambulatory setting and need the study participants to be available for at least 3 hours and 5 minutes, not including the optional blood marker sampling (blood: 15 min, CSF: 30 min). To evaluate the association between the onset and severity of both motor and non-motor symptoms which might indicate disease progression and are therefore more pronounced in PD patients with mild ADL dysfunction, a comprehensive clinical assessment will be conducted.

- If patients agree to the optional CSF and/or blood collection (see also 8.6):
  - Blood collection 15 min
  - CSF 30 min

  Total time for biomarker sampling: **45 min**

Caregiver assessments:

To validate the patient's self-impression, the following caregiver questionnaires and interview scales will be applied, needing caregivers to be available for at least 40 minutes. Caregiver assessments will only be performed if the respective patient has agreed to the interview.

Table 2: Overview of caregiver assessments

Assessment	Time
Explanation of the study requirements	10 min
Interview-based ratings:	
Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE)	6 min
Tübinger Activity of Daily Living Inventory for Parkinson's disease	6 min
Questionnaires:	
Pfeffer Functional Activities Questionnaire (FAQ)	4 min
Bayer Activities of Daily Living Scale (Bayer ADL)	5 min
Top-10 Priority List	5 min
Saarbrücker Persönlichkeitsfragebogen (SPF)/ Interpersonal Reactivity Index (IRI)	4 min
Total Time of caregiver assessment:	**40 min**

8.1. Retrospective Data

Data collected in the clinical routine, e.g. demographics, medication intake, concomitant diseases and procedures, disease and motor severity, detailed neuropsychological assessments, and detailed non-motor symptom assessments, will be included in the data analysis. If these parameters are collected when participating in other clinical studies, these will also be included.

8.2. Neuropsychological testing

The aim is to diagnose PD-MCI and PDD according to the Level-II recommendations of the Movement Disorder Task Force [9, 10, 12]. Therefore the following five domains will be quantitatively assessed using the Consortium to Establish A Registry of Alzheimer' Disease (CERAD-Plus) battery, three subtests of the Wechsler Intelligence Tests for Adults (WIE), and one subtest of the Leistungsprüfsystem für 50- bis 90-Jährige (LPS50+). At least two tests are assigned to each cognitive domain:

- Executive functions: Lexical and phonemic fluency (CERAD-Plus), Trail Making Test Part B
- Attention/working memory: Digit-Symbol Test (WIE), Letter-Number Sequencing (WIE)
- Language: Boston Naming Test (CERAD-Plus), Similarities (WIE)
- Memory: Word List learning, recall, and discriminability (CERAD-Plus) and Praxis recall (CERAD-Plus)
- Visuospatial abilities: Praxis (CERAD-Plus), Fragmented Words (LPS-50+)

The MMSE included in the CERAD-Plus, as well as the Montreal Cognitive Assessment will serve as global cognitive screening scales.

8.3. Comprehensive non-motor symptom assessment and Top-10 Priority List

The occurrence and progression of non-motor symptoms is known to be associated with a more rapid cognitive decline as well as dementia in PD [1]. Therefore, we aim to assess the most common non-motor symptoms in PD, especially those symptoms that increase the risk for cognitive worsening and PDD (e.g. hallucination, anxiety, depression, and apathy) [5, 12]. Most of the symptoms will be assessed by patient self-questionnaires, which can be filled out at home if the assessment in the clinic is too stressful for the patients.

Information from the questionnaires will be used to identify those symptoms associated with a worsening of cognitive-driven ADL function and cognition in our sample, which might further help to characterize those PD patients with a potentially high risk for the development of PDD.

Data of the Top-10 Priority List, in addition to selected clinical data, will be shared for clinical research purposes with Oxford University Associate Professor Michele Hu, and University of Luxembourg Professor Reijko Krüger, within the H2020-TWINN-2015 project (research receives no special funding within this grant). The aim of this subproject is to ascertain PD patients' priorities for future research aims, giving insight into their special needs and hopes for future research. Aim of the three centres' collaboration is two-folded: first to compare the priorities of PD patients, caregivers, and nurses among different countries (no additional information needed), and second to link the results of the Top-10 Priority List to the individual data assessed, including the clinical symptom profile and correspondence between patient and caregiver responses. Within the consent form, patients and caregivers will be asked about the possibility of sharing psedudonymized data with the collaboration partners.

8.4. Home-based movement assessment (Accelerometer)

Physical activity directly influences health-related quality of life in PD [28], with specific aspects of physical activity decreasing with the severity of cognitive impairment [29]. We will therefore conduct a home-based movement assessment in a random subgroup of patients, to examine the influence of physical activity on cognition and other non-motor symptoms in PD. Participants will be asked to wear an accelerometer (MoveMonitor, McRoberts, The Netherlands) on their lower back for 7 consecutive days in their home environment. The accelerometer is capable of data uptake for 7-10 days, and assesses various movement parameters (e.g. time spent sitting, lying, walking, and standing, as well as step count).

8.5. Caregiver ADL assessments

Caregiver assessments have a crucial role determining a diagnosis of PDD, by examining whether patients are able to care for themselves and carry out their daily activities. The Bayer Activities of Daily Living (Bayer ADL) scale consists of 25 questions answered by the caregiver that evaluate the patient's ability to perform activities of daily living. The Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE), a brief screening tool of dementia, compares patients' current abilities to how they were two years ago. This provides a useful marker for cognitive ADL progression, as well as helps to distinguish cognitive decline from normal aging. The caregiver assessment of ADL using the FAQ allows us to compare patient and caregivers' evaluation of ADL impairments.

8.6. Biomaterial collection

8.6.1. CSF and blood collection

Blood collection: Serum (about 89 ml) will be collected for routine analyses in the Zentrallabor and the Neurochemisches Labor of the Universitätsklinikum Tübingen (UKT), for targeted biomarker search, for explorative proteomic and metabolomics approaches, as well as for the determination of genetic markers (APOE Genotype, MAPT, COMT, and GBA). This amount does not represent any health hazard. Blood samples will be collected in the morning, on an empty stomach.
Through venipuncture, the following samples will be taken for analysis and will remain in the Hertie Institut für klinische Hirnforschung (Ethic Proposal: 199/2011BO1):

- 10 ml venous blood for the determination of routine values in the Zentrallabor (1 Serum tube)
- 3 ml of venous blood (1 PaxGene tube) for RNA Isolation
- 20 ml of venous blood in 2 large EDTA tubes
- 10 ml of venous blood in 1 Serum tube

CSF collection: The lumbar puncture at level L3/L4 or L4/L5 of the spine will be performed by a qualified clinician. The applicants have extensive experience with this procedure (see e.g. Ethical proposals 46/2010 and 404/2010). Subjects will be closely monitored during and after the procedure. Up to 15 ml of CSF will be collected unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. This amount does not represent any health hazard. The first 2 ml of CSF will be processed at the Zentrallabor to conduct standard analyses on cell count, protein, and glucose levels, while another aliquot will be sent to the Neurochemisches Labor to conduct analyses of neurodegenerative markers such as Abeta1-42 and Abeta1-40.

8.6.2. Tissue collection

Not applicable.

8.6.3. Analysis of biomaterial

A structured and integrated exploration of biomaterial in combination with the analysis of the extensive quantitative dataset obtained in this study bears the chance for a better molecular,

biochemical, and eventually functional understanding of one of the most debilitating symptoms associated with PD, i.e. cognitive deterioration.
For all patients, DNA, CSF, and plasma were sampled at baseline. Using the NeuroChip, patients were screened for genetic variants associated with dementia and PD. CSF levels of Aß1-42, phosphor- and total Tau were determined within the frame of the ABC-PD study.
In collaboration with the company ADX, represented by Hugo Vanderstichele and Erik Stroops, the following baseline CSF biomarkers were provided for further analysis of 200 patients: Aß1-42, Aß1-40, Aß1-38, phosphor Tau 181, NF heavy, neurogranin, BASE-1, and alpha-synuclein. Thus, biomaterial will be primarily analysed locally, but will also be shared with non-profit research organisation partners such as ADX.
At time of follow-up, a maximum of 100 PD patients are expected to give a second CSF sampling. Levels of CSF biomarkers indicating cognitive worsening [30-35] will be measured using the solid phase enzyme essays from Fujirebio Germany GmbH: Aß1-42, Aß1-40, phosphor- and total Tau.

8.6.4. Storage of biomaterial

All samples will be stored at -80°C until use. To maximize confidentiality, all biomarker samples and information associated with the samples will be coded to prevent the exposure of the subject's information and identity. This coding process allows location and destruction of a sample at the subject's request. In addition, sample information is stored in one secured electronic database, while biomarker data is stored in an independently secured database on a different computer. No one except the investigators of the UKT will have access to the database to deduce the identity of the patient.

9. Risks and possible adverse reactions, end of the study

9.1. Neuropsychological testing

No relevant risks.

9.2. Comprehensive non-motor symptom assessment and Top-10 Priority List

No relevant risks.

9.3. Home-based movement assessment (Accelerometer)

No relevant risks.

9.4. Caregiver ADL Assessments

No relevant risks.

9.5. Biomaterial (Blood and CSF) collection

Venipuncture is usually well tolerated and is rarely associated with complications. However, at the site of injection it may cause symptoms such as bruising, small scars, induration, abnormal sensations around the puncture due to unintentional nerve injury (median nerve in

some cases with long-lasting sensory and motor deficits), infection, phlebitis (thrombophlebitis), a thrombosis, or it can wash away the smallest blood clots (embolisms). Circulatory reactions (so-called vagovasal reactions) can also occur. However, complications of this kind have rarely occurred so far.
Lumbar puncture is a routine assessment in neurological hospitals. The risk of injury of nerves, bones or other viscera is possible in theory but is extremely unlikely because of atraumatic injection needles. The needle prick can hurt locally and, in 10 percent of cases, radiating in the legs due to touching one of the lumbal nerve roots may occur for the fraction of a second. In theory, a local hemorrhage or an infection is possible. However, this has never occurred during the thousands of lumbar punctures performed every year at the Neurology Department of the UKT in the context of diagnostic measures ever since atraumatic needles have been available. During a period of hours to days, headaches can occur in an upright position. In very rare cases, it can cause patients to become bedridden for several days, a clear indication for a blood patch. A blood patch is another “lumbar puncture” at the place where the first puncture was performed, without collection of CSF but this time injecting autologous blood into the tissue *without penetrating* the dura mater again. It is hypothesized that this procedure closes the hole leading to CSF leakage. Ever since the introduction of atraumatic needles, the frequency of post-puncture headache in people older than 50 years has decreased substantially and is now below 2% [36].

9.6. End of the study

December 2020.

10. Data protection

10.1. Data collection

Data collection and use of personally identifiable information for this study complies with the General Data Protection Regulation (EU) 2016/679. Participants will be given the appropriate information on dealing with data collected in the study and asked to sign a separate informed consent form concerning data protection.

10.1.1. Which data are collected; is it possible to identify the donor?

Data of every subject – name, age, disease duration, as well as all assessed parameters and results of the biomarker assessments – are collected in separate folders, and will be stored in a lockable office of the PI or his/her representative. As a database platform, the REDCap electronic data capture tool will be used [37]. The database will be secured with password protection, individually assigned to each team member with database access. Pseudo-anonymized data will be saved in the database inside the firewall of the medical faculty, using a 4-digit number not associated with any demographics of the study participant. Thus, the identification of a participant using only the code number is not possible and confidentiality will be ensured by use of these identification codes. The informatics manager and PI will only receive coded information that has been entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information.

10.1.2. Shall patients be informed about novel scientific findings?

If participants wish to be informed about their individual CSF Abeta1-42 results (as per indication on the ABC-PD cross-sectional patient consent form (ethic protocol 686/2013B01)), this will take place during a one-on-one consultation with the PI/representative. If the patient agrees, he/she will be informed about the cognitive outcome. Beyond these specific parameters, it is not planned to keep the participants informed about the individual study results.

10.1.3. Period of data storage

Data will be stored for 10 years.

10.1.4. Erasure of personal data

Participants have the right to gain information about stored data, to correct false data, to demand the erasure of personal data, and to demand the anonymization of their data. The PI of the study PD Dr. Inga Liepelt-Scarfone (phone: +497071-2980424, Fax: +497071-294490, E-mail: inga.liepelt@uni-tuebingen.de) and Dr. Kathrin Brockmann (phone: +497071-2980171; Fax: +497071-2925195, E-mail: kathrin.brockmann@uni-tuebingen.de) are responsible for the adherence of all law regulations.
Contact information: Hertie Institute for Clinical Brain Research, Department of Neurodegeneration, University of Tübingen, Hoppe-Seyler Str. 3, 72076 Tübingen, Germany.

10.2. Transfer of data to the Sponsor

De-identified clinical data may be shared with The Michael J. Fox Foundation for Parkinson's Research (the study funder, Grant ID: 15227; Grand Central Station, P.O. Box 4777, New York, NY 10163-4777. Tel: +1-800-708-7644). This data may be kept for storage at a central repository hosted either by The Michael J. Fox Foundation, its collaborators, or consultants, and will be kept indefinitely. In order to advance scientific discoveries, the de-identified data will be made publically available (with no personal identifying information) for the intended use of research in PD as well as other biomedical research studies that may not be related to PD. This is clearly stated in the patient and caregiver informed consent forms.

10.3. Information and informed consent

Prior to the respective assessments, every prospective participant will be informed in oral and written form about the general goal of the study and how the assessments will be performed. In particular, the informed consent form will contain comprehensive information about contents, objectives, duration, procedures, voluntariness, and possible risks of the study participation. Any kind of questions will be considered and answered. In case of agreement for study participation, the participant has to sign two copies of the informed consent form. One will be given to the participant, and the other form will be stored at the local study centre in a separate folder (not in the medical records).
In addition to the PD patients, a caregiver will be contacted and interviewed. Therefore, informed consent will also be obtained from the patient's caregiver using a separate caregiver

informed consent form. The patient will be asked to choose the caregiver who will then be contacted for the caregiver assessment.

11. Insurance

The study is covered by the clinical trials insurance. No travel accident insurance will be offered. However, for CSF sampling, patients will be additionally insured to increase their safety in case of the above mentioned adverse events (AEs) or serious adverse events (SAEs) after lumbar puncture. SAEs are unanticipated, serious, and possibly related to the study procedures. SAEs will be reported to the local ethical committee in accordance with requirements. An appropriate application for a selected insurance will be filed with the help of the insurance management (contact person: Mrs. Iris Wolf) of the University of Tübingen. The insurance confirmation and the insurance conditions will be passed on to the Ethics Committee after the insurance has been taken out. The patient information is also provided with the most important information (contents and exclusions of the insurance, compensation amount, period of insurance, name and contact details of the insurer, insurance certificate number, obligations of the insured according to the insurance conditions) and the insurance confirmation and the insurance conditions are attached to the subject information as soon as they are available.

Number of insurance police: 57 010311 03013
Insurance Period: 15.08.2018 until 31.12.2020
Amount of damage compensation: 500,000.00€ per participant, Maximum limit of indemnity is 5,000,000.00€ (for all 209 participants).

12. Information text and text of the informed consent

See attachments:

- Patient information sheet and informed consent form
- Patient data privacy statement
- Caregiver information sheet and informed consent form
- Caregiver data privacy statement

13. Reference list

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