# Parkinson's Disease: Evolution of cognitive impairment and CSF $Abeta_{1\_42}$ profiles in a prospective longitudinal study

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**Abstract**

**Background:** Prediction of the slope of cognitive deterioration in Parkinson‘s disease (PD) is important for subgroup-specific treatment. Besides Lewy body pathology, Amyloid-β (Aβ) and Tau pathology have been discussed as potential modifying agents and are reflected by altered cerebrospinal fluid (CSF) levels of $A\beta_{1-42}$, total-Tau (t-Tau) and phosphorylated-Tau (p-Tau).

**Objective:** To evaluate the evolution of cognitive impairment in relation to CSF profiles in PD.

**Methods:** Prospective, longitudinal, observational study up to 10 years with follow-up every two years. We assessed CSF profiles in 415 sporadic PD patients (median age 66; 63% male) and 142 healthy controls (median age 62; 43% male).

**Results:** PD patients with low CSF $A\beta_{1-42}$ levels at baseline were more often cognitively impaired than patients with intermediate and high $A\beta_{1-42}$ levels. Sixty-seven percent of the patients with low $A\beta_{1-42}$ levels at baseline and normal cognition developed cognitive impairment during follow-up, compared to 41% and 37% of patients having intermediate and high CSF $A\beta_{1-42}$ levels. Kaplan Maier Survival Curves and Cox Regression revealed that patients with low CSF $A\beta_{1-42}$ levels at baseline developed cognitive impairment more frequently and earlier during follow-up.

**Conclusion:** $A\beta_{1-42}$ CSF profiles in PD patients might be useful for predicting phenotypic variability concerning cognitive deterioration.

## Introduction

Parkinson's disease (PD) is a complex disorder with multifactorial etiology, heterogeneity in phenotypes and variability in progression of motor and non-motor symptoms. This calls for prediction and progression biomarkers in order to monitor the course of neurodegeneration, and to establish endpoints for therapeutic strategies aiming to modify disease progression.

A possible explanation for the clinical variability in PD patients might be an inter-individual heterogeneity in the underlying pathogenesis and pathologic processes [1, 2]. In addition to the typical Lewy body pathology, a considerable proportion of patients have β-amyloid (Aβ) and Tau pathology at autopsy, predominantly presenting a clinical phenotype with dementia in their disease course [3, 4]. Several studies have reported altered CSF levels of $A\beta_{1\text{-}42}$, total-Tau (t-Tau) and phosphorylated-Tau (p-Tau) in sporadic PD patients. The most robust results indicate decreased levels of $Abeta_{1\_42}$ to be associated with cognitive impairment [5-10]. However, longitudinal data of these protein levels in CSF and its evolution over the course of the disease are rather limited. Additionally, it is unclear to what degree these protein alterations are involved in PD pathogenesis or rather represent concomitant pathology or aging processes and whether they are influenced by genetic variation. In the era where disease-modifying treatment options are starting to emerge, these gaps need to be filled in order monitor and dissect disease progression and treatment effects.

## Participants and Methods

*Participants*

All PD patients reported in this study were recruited between 2003 and 2017 and are patients of the ward and/or outpatient clinic for PD at the University Hospital Tuebingen. Some of them are participants of PD-related clinical prospective longitudinal studies of our Department [11, 12]. Spouses and relatives of PD patients and volunteers recruited by newspaper advertisements were assessed and only those with no indication for a neurodegenerative disease were selected

as healthy control individuals (CON). All PD patients were controlled to have no p.G2019S *LRRK2* mutation or one of the most frequent *GBA* mutations (p.L444P; p.N370S, p.E326K). Moreover, patients were screened for mutations in *Parkin* and *PINK1* if the following criteria were fulfilled: age of onset ≤ 40 years or a positive family history compatible with a recessive mode of inheritance. In total, CSF data from 415 PD patients and 142 CON participants were available for the cross-sectional analysis. Of the 415 participants with PD, 274 completed a 2-year, 162 a 4-year, 76 a 6-year, 36 an 8-year, and 19 a 10-year follow-up of clinical assessment and partially also of lumbar puncture.

*Clinical Investigations*

At each time point, all subjects including the healthy controls were examined by a neurologist (DB, FB, KB, GM, WM, BR, IW, MZ) blinded to the results of the CSF marker analysis. PD patients were assessed in the dopaminergic ON state. Diagnosis of PD was defined according to UK Brain Bank Society Criteria [13]. We assessed severity of motor symptoms using part III of the Unified Parkinson's disease Rating Scale (UPDRS-III from 2003-2008, MDS-UPDRS from 2009 on [14]). Disease stage was categorized by the modified Hoehn and Yahr Scale (H&Y) [15]. Cognitive function was tested using the Montreal Cognitive Assessment (MoCA) [16] and/or the Mini Mental Status Examination (MMSE) [17]. Since the MoCA was only available from 2009 on, we converted the MMSE scores into MoCA equivalent scores according to the algorithm published recently [18]. Hence, a valid MoCA score was available for each subject at each time point. A MoCA cut off ≤25 was used as the point for maximum combined sensitivity and specificity for cognitive impairment [19].

*Collection of CSF samples and CSF Marker Analysis*

CSF collection and determination of routine diagnostic parameters were performed according to standardized protocols [20]. In brief, spinal tap was performed between 9.00am and 1.00pm.

Individuals were in a sitting position and the needle was tapped in the L3-4 or L4-5 interspace. Samples were directly taken from the bedside and centrifuged within 30 minutes after collection and frozen at −80°C within 60 minutes after collection. Only samples of subjects with normal routine CSF diagnostics (white blood cell count <4*106/l, IgG index <0.6) were included. CSF levels of $A\beta_{1-42}$, t-Tau and p-Tau (phosphorylated at T181) were measured in Tuebingen using commercially available ELISA kits (INNOTEST; Fujirebio Germany GmbH, Hannover, Germany). The antibodies bind specifically to the sequences MVGGVV (first antibody: 21F12) and DAEFRH (second antibody: 3D6), detecting Aβ right from the first amino acid. The measurements were performed by board-certified laboratory technicians who were blinded to clinical data. To check for longitudinal stability of the measurements, two internal longitudinal quality control samples (QC) were run on each plate (supplemental Table 1). The intra-assay coefficients of variation for each CSF parameter were below 15%. Quality data of the Tuebingen laboratory within this program can be found in supplemental Table 2. The Tuebingen laboratory is part of the Alzheimer's Association Quality Control Program for CSF Biomarkers [21].

For further subgroup analysis, PD patients were classified based on their individual baseline levels of CSF $A\beta_{1-42}$ according to internal standards and similar to Palmqvist et al.[22] into the following groups: high: ≥ 600pg/ml, intermediate: 599-300 pg/ml and low: <300 pg/ml.

*Genetics*

All samples were genotyped using the Illumina Neurochip array (ref: PMID:28602509). Genotypes for the APOE haplotype (rs429358 and rs7412) were extracted from the larger dataset. The SNPs were in HWE (p=0.07 and p=0.49).

*Statistics*

Statistical analysis was performed using IBM SPSS 22.0 software for Windows SPSS (Inc, Chicago, IL, USA).

1. *Cross-sectional comparisons* of demographic, clinical and CSF markers between PD and CON at baseline were calculated by ANOVA. Dichotomous data were analyzed using the Fisher Exact Test. Differences were considered significant at $p < 0.05$.

2. *Multiple linear regression analyses* were used to evaluate independent effects of demographic and clinical data at baseline (independent variables: age, gender, disease duration, CSF levels of $A\beta_{1-42}$, t-Tau and p-Tau) on MoCA scores (dependent variable) in PD patients for each time point. Differences were considered significant at $p < 0.05$.

3. *Kaplan Mayer survival curves and Cox proportional hazard models* stratified by the $A\beta_{1-42}$ subgroup (high vs. median vs. low) were used to estimate disease duration free from cognitive impairment (MoCA≤25) in PD patients. Time to event was defined as disease duration until first clinical diagnosis of cognitive impairment. Risk of development of cognitive impairment was calculated with Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) and p-values for pairwise comparisons.

*Protocol Approvals and Patient Consents*

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Tuebingen (199/2011BO1). All participants gave written informed consent.

## Results

*1. Inter-group characteristics*

Baseline characteristics of demographic and clinical data stratified by cohort are shown in Table 1. PD patients were older, more often male and had lower MoCA scores compared to CON. Within the PD group, those with cognitive impairment were older at disease onset and at clinical

visit and had higher (MDS-)UPDRS-III scores and higher H&Y stages compared to PD patients with normal cognitive profiles ($p<0.001$ respectively).

*2. Association between demographic data, clinical characteristics and CSF levels with MoCA scores in PD patients*

Higher age and longer disease duration were associated with lower MoCA scores at baseline (age: $p<0.001$; disease duration: $p<0.001$), after two years (age: $p<0.001$; disease duration $p<0.001$), after four years (age: $p<0.001$; disease duration: $p=0.014$) and after six years (age: $p=0.033$; disease duration: $p=0.001$). Lower CSF $A\beta_{1-42}$ levels were associated with lower MoCA scores at baseline, after two years and after four years (baseline: $p=0.004$, two years: $p=0.046$, four years: $p=0.050$). Male gender was associated with lower MoCA scores after eight years ($p=0.040$). No association were found for CSF levels of t-Tau and p-tau with MoCA. For details see Table 2.

*3. Progression to cognitive impairment in relation to CSF Abeta$_{1_42}$ levels*

*a) Kaplan Mayer survival curves and Cox proportional hazard models stratified by CSF A$\beta_{1-42}$ subtype with development of cognitive impairment as outcome*

Participants classified as "low CSF $A\beta_{1-42}$ subgroup" (<300 pg/ml) had a higher risk of developing cognitive impairment (HR (95% CI) = 1.66 (1.27-2.18); $p<0.001$) and developed cognitive impairment earlier in the disease course compared to those classified as intermediate and high CSF $A\beta_{1-42}$ subgroup (5.9 years disease duration vs. 9.8 and 10.5 years disease duration; $p=0.006$) (Figure 1 and 2).

*b. Demographics and development of cognitive impairment based on CSF A$\beta_{1-42}$ subtype*

PD patients with low $A\beta_{1-42}$ levels (<300pg/ml) were older at disease onset and older at baseline study visit. They had lower MoCA scores and were more often cognitively impaired at baseline compared to patients with intermediate and high levels of $A\beta_{1-42}$. Of those patients classified as

"low CSF $A\beta_{1-42}$ subgroup" and who were not cognitively impaired at baseline, 67% developed cognitive impairment during follow-up compared to 41% and 37% of PD patients classified as intermediate and high CSF $A\beta_{1-42}$ subgroup (p=0.038) (Table 3). The observation interval for those PD patients not reaching the milestone "cognitive impairment" was 4 ± 1 years (<300 pg/ml), 8 ± 4 years (599-300 pg/ml) and 9 ± 4 years (≥600 pg/ml).

*c. Demographics and clinical characteristic of PD patients who newly developed cognitive impairment compared to those free from cognitive impairment at last clinical follow-up visit.*

During the observation period, 65 PD patients newly developed cognitive impairment (42 at 2-years, 13 at 4-years, 10 at 6-years). This subgroup was older at disease onset, older at baseline study visit, had lower MoCA scores and higher H&Y stages at baseline, compared to those patients free from cognitive impairment at last clinical follow-up visit. See Figure 1-part B and Table 4.

*4. Association of APOE genotype with CSF $A\beta_{1-42}$ levels in PD patients*

PD patients with at least one *APOE* ε4 allele had lower CSF levels of $A\beta_{1-42}$ compared to patients with no *APOE* ε4 allele ($A\beta_{1-42}$: 577 pg/ml vs. 732 pg/ml; p<0.001). As the number of PD patients carrying two *APOE* ε4 alleles was small (n=7), we did not perform a separate statistical analysis. PD patients with at least one *APOE* ε4 allele did not differ in demographics and clinical characteristics compared to those patients with no *APOE* ε4 allele (Table 5).

## Discussion

The clinical presentation of motor and non-motor symptoms and the prognostic outcome of PD are highly variable. There is increasing evidence that proteins such as $A\beta_{1-42}$ and Tau indicate the presence of disease modifiers and thereby explain part of the variety of the clinical phenotype [3, 4, 23].

By examining CSF $A\beta_{1-42}$, t-Tau and p-Tau levels ***cross-sectionally*** in sporadic PD patients, we could show that: (I) Higher age, longer disease duration and lower levels of $A\beta_{1-42}$ were associated with worse cognitive performance assessed by the MoCA; (II) PD patients with low $A\beta_{1-42}$ levels were more frequently cognitively impaired at baseline and more often developed cognitive decline during the observation period; (III) presence of at least one *APOE* ε4 allele is associated with lower CSF levels of $A\beta_{1-42}$ in PD patients.

By assessing CSF levels of $A\beta_{1-42}$, t-Tau and p-Tau ***longitudinally***, we could confirm main findings from the cross-sectional analyses: (I) Higher age, longer disease duration and lower levels of $A\beta_{1-42}$ were associated with worse cognitive performance assessed by the MoCA at two, four and six years of follow-up; (II) Lower levels of $A\beta_{1-42}$ were associated with a higher proportion of PD patients developing cognitive impairment earlier during the disease course.

Evidence that proteins such as Aβ act as disease modifiers comes not only from genetic but also from histopathological studies: a considerable proportion of sporadic PD patients who displayed concomitant AD pathology at autopsy, in addition to the expected Lewy body pathology, presented with dementia before death [2, 3, 24]. The association of reduced $A\beta_{1-42}$ levels with PD-associated dementia is in line with findings from several cross-sectional studies [8, 25, 26] and a limited number of longitudinal investigations [27-29]. Therefore, CSF profiles of $A\beta_{1-42}$ might be useful for monitoring phenotypic variability with focus on cognitive impairment in a subgroup of PD patients.

However, at this point, we know little in terms of the timely and quantitative evolution of CSF Aβ profiles in relation to the development of cognitive decline in PD. When does a decrease of CSF $A\beta_{1-42}$ in relation to the onset of PD-associated cognitive decline occur and what might be the best diagnostic cut-off for clinical routine? Do we need age-dependent and disease-specific cut-offs? Studies in inherited forms of Alzheimer's disease report a sequential occurrence of different biofluids, imaging and clinical markers. In this context, the reduction of CSF $A\beta_{1-42}$

levels seems the earliest marker and occurs about 25 years before the expected clinical symptom onset [30].

It would also be interesting to know to what degree genetic variation promotes pathologic aggregation of different protein species possibly reflected by CSF profiles. There is evidence that the *APOE* ε4 allele promotes Aβ pathology [31] and consecutively is associated with reduced CSF levels of $A\beta_{1-42}$ and an increased risk of developing PD-associated cognitive decline as shown in the present study as well as reported by others and even in the PPMI study in early stage PD patients [32, 33].

A strength of our study is the measurement of CSF $A\beta_{1-42}$ levels in a large monocentric longitudinal cohort according to standardized operating procedures (SOP) of clinical assessments and sample preparation and biomarker analyses[27]. It has been shown that large multicenter cohorts might face the problem that site-specific effects can pose an important confounder despite given SOPs for clinical and biomaterial work-up.

Limitations of the present study are as follows: (I) With increasing follow-up time, especially patients with cognitive decline dropped out of the study limiting the validity of CSF levels especially at later stages of the long follow-up period. (II) Although converting scales for MMSE into MoCA are available, both tests do not exactly capture the same cognitive domains to the same amount (e.g. MoCA captures better executive dysfunction whereas MMSE focuses on memory and orientation) and both have different ceiling effects. More sophisticated clinical assessments are in need in order to evaluate distinct cognitive domains in relation to CSF profiles.

We conclude that in sporadic PD patients, low levels of $A\beta_{1-42}$ are associated with a higher risk of developing cognitive impairment earlier in the disease process at least in a subgroup of patients.

**Author Contributions:**

KB, DB, TG, and WM designed the study. IW, BR, GM, MZ, FB, ES, CD, CS, DB, WM, and KB collected data. ES performed the immuno-assays for CSF measurements. SL performed the statistical analysis and drafted the manuscript. All authors were involved in interpretation of the data and critical revision of the manuscript. All authors gave their final approval.

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**Dr. Gasser** serves on the editorial boards of Parkinsonism and Related Disorders, Movement Disorders, and Journal of Neurology; holds a patent re: KASPP (LRRK2) Gene, its Production and Use for the Detection and Treatment of Neurodegenerative Diseases; serves as a consultant for Cephalon, Inc. and Merck Serono; serves on speaker's bureaus of Novartis, Merck Serono, SCHWARZ PHARMA, Boehringer Ingelheim, and Valeant Pharmaceuticals International; and receives research support from Novartis, the European Union, BMBF (the Federal Ministry of Education and Research), and Helmholtz Association.

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## Tables

**Table 1: Clinical characteristics of healthy controls and PD patients at baseline**

| | Healthy controls n=142 | PD patients n=415 | p-value | PD patients cognitively normal n=225 | PD patients cognitively impaired n=182 | p-value |
|---|---|---|---|---|---|---|
| Male gender, n (%) | 67 (47) | 260 (63) | 0.001 | 140 (62) | 116 (64) | 0.758 |
| Age [years] | 62 ± 12 | 66 ± 10 | <0.001 | 63 ± 9 | 70 ± 8 | <0.001 |
| Age at onset [years] | - | 60 ± 10 | | 58 ± 9 | 63 ± 10 | <0.001 |
| Disease duration [years] | - | 6 ± 5 | | 6 ± 4 | 8 ± 5 | <0.001 |
| MoCA (0-30) | 28 ± 2 | 25 ± 4 | 0.034 | 28 ± 1 | 21 ± 4 | <0.001 |
| UPDRS-III (0-163) | - | 26 ± 12 | | 23 ± 10 | 29 ± 13 | <0.001 |
| H&Y (0-5) | - | 2 ± 1 | | 2 ± 1 | 2 ± 1 | <0.001 |

Abbreviations: H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale part 3. Data are shown as mean and standard deviation or N (%). n=8 PD patients with missing baseline MoCA scores.

**Table 2: CSF levels of Abeta$_{1_42}$, t-tau, p-tau and demographics as predictors of MoCA scores in PD patients**

| | BL | 2 years | 4 years | 6 years | 8 years |
|---|---|---|---|---|---|
| Independent variables | n=377 | n=215 | n=131 | n=63 | n=24 |
| Gender | 0.008 | 0.002 | -0.095 | -0.129 | **-0.401*** |
| Age [years] | **-0.382***** | **-0.313***** | **-0.436***** | **-0.247*** | -0.229 |
| Disease duration [years] | **-0.197***** | **-0.247***** | **-0.193*** | **-0.399**** | **-0.680**** |
| CSF Abeta$_{1-42}$ [pg/ml] | **0.133**** | **0.110*** | **0.149*** | 0.091 | 0.293 |
| CSF total-Tau [pg/ml] | -0.011 | -0.001 | -0.011 | 0.173 | 0.241 |
| CSF phospho-Tau [pg/ml] | -0.033 | -0.081 | -0.017 | 0.162 | 0.256 |

Abbreviations: CSF, Cerebrospinal fluid. Data are shown as standardized beta coefficients.
*p<0.05;**p<0.01;***p<0.001

**Table 3: Clinical characteristics and development of cognitive impairment in PD patients stratified by CSF Abeta$_{1-42}$ subgroup at baseline**

| | Abeta$_{1-42}$ >600 pg/ml n=247 | Abeta$_{1-42}$ 599-300 pg/ml n=148 | Abeta$_{1-42}$ <300 pg/ml n=20 | p-value |
|---|---|---|---|---|
| Male gender, n (%) | 157 (64) | 92 (62) | 11 (55) | 0.740 |
| Age [years] | 66 ± 10 | 67 ± 9 | 72 ± 6*# | 0.012 |
| Age at onset [years] | 59 ± 10 | 60 ± 10 | 68 ± 6*# | <0.001 |
| Disease duration [years] | 7 ± 5 | 7 ± 5 | 5 ± 4 | 0.277 |
| MoCA (0-30) | 25 ± 4 | 24 ± 5 | 21 ± 5*# | <0.001 |
| UPDRS-III (0-163) | 26 ± 10 | 26 ± 14 | 26 ± 15 | 0.751 |
| H&Y (0-5) | 2 ± 1 | 2 ± 1 | 2 ± 1 | 0.211 |
| Cognitively impaired at baseline, n (%) | 95 (38) | 74 (50)* | 13 (65)* | 0.004 |
| Development of cognitive impairment during observation period , n (%) | 41/101 (41) | 20/54 (37) | 4/6 (67)*# | 0.038 |

Abbreviations: CSF, Cerebrospinal fluid; H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale part 3. Data are shown as mean and standard deviation or N (%).

* significant <300pg/ml versus ≥600 pg/ml; # significant <300pg/ml versus 599-300 pg/ml

**Table 4: Baseline clinical characteristics and CSF Abeta$_{1_42}$ levels in PD patients who newly developed cognitive impairment during follow up compared to those free from cognitive impairment**

| | No cognitive impairment during observation period n=97 | Development of cognitive impairment during observation period n=65 | p-value |
|---|---|---|---|
| Male gender, n (%) | 61 (62) | 42 (65) | 0.868 |
| Age [years] | 63 ± 9 | 67 ± 9 | 0.006 |
| Age at onset [years] | 58 ± 9 | 61 ± 9 | 0.024 |
| Disease duration [years] | 5 ± 4 | 6 ± 4 | 0.323 |
| MoCA (0-30) | 28 ± 1 | 27 ± 1 | 0.017 |
| UPDRS-III (0-163) | 23 ± 9 | 24 ± 11 | 0.339 |
| H&Y (0-5) | 2 ± 1 | 2 ± 1 | 0.030 |
| CSF Abeta $_{1-42}$ [pg/ml] | 720 ± 253 | 702 ± 259 | 0.816* |

Abbreviations: CSF, Cerebrospinal fluid; H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale part 3. Data are shown as mean and standard deviation or N (%). * p-value corrected for age.

**Table 5: Baseline demographics, clinical characteristics and CSF profiles of PD patients stratified by *APOE* genotype**

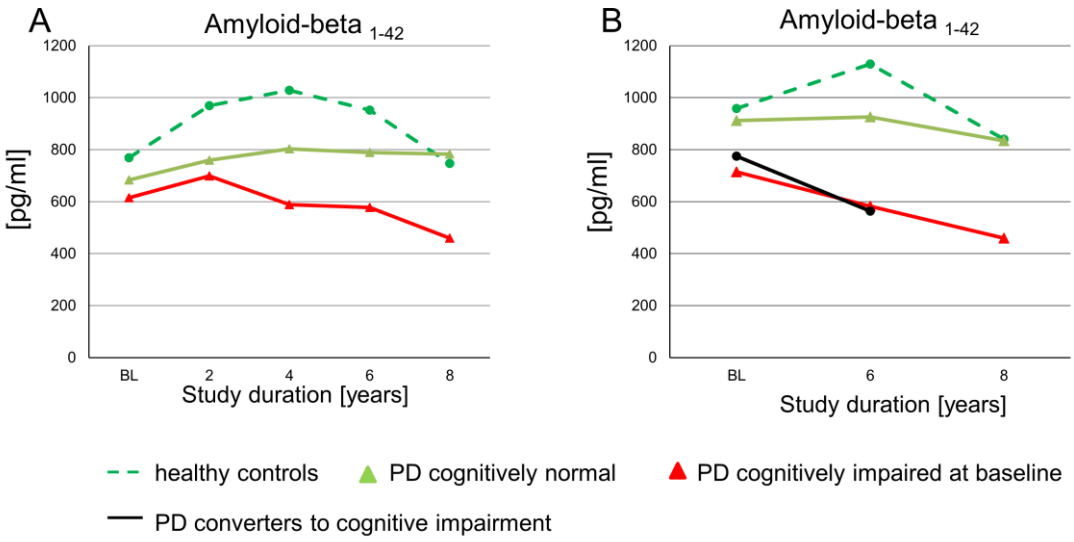
| | One *APOE* ε4 n=91 | Two *APOE* ε4 n=7 | At least one *APOE* ε4 n=98 | No *APOE* ε4 n=301 | p-value |
|---|---|---|---|---|---|
| Male gender, n (%) | 52 (21) | 4 (2) | 56 (22) | 195 (78) | 0.187 |
| Age [years] | 65 ± 10 | 65 ± 6 | 65 ± 10 | 66 ± 10 | 0.136 |
| Age at onset [years] | 58 ± 9 | 59 ± 7 | 58 ± 9 | 60 ± 10 | 0.124 |
| Disease duration [years] | 7 ± 5 | 7 ± 5 | 7 ± 5 | 6 ± 5 | 0.852 |
| MoCA (0-30) | 25 ± 4 | 25 ± 4 | 25 ± 4 | 25 ± 4 | 0.600 |
| UPDRS-III (0-163) | 25 ± 12 | 24 ± 15 | 25 ± 12 | 26 ± 11 | 0.495 |
| H&Y (0-5) | 2 ± 1 | 2 ± 1 | 2 ± 1 | 2 ± 1 | 0.835 |
| CSF Abeta $_{1-42}$ [pg/ml] | 583 ± 223 | 500 ± 191 | 577 ± 222 | 732 ± 277 | <0.001 |
| CSF total-Tau [pg/ml] | 244 ± 147 | 239 ± 123 | 243 ± 145 | 247 ± 143 | 0.841 |
| CSF phosphorylated-Tau [pg/ml] | 42 ± 20 | 42 ± 16 | 42 ± 19 | 43 ± 18 | 0.580 |
| Cognitively impaired at baseline, n (%) | 31 (35) | 4 (57) | 35 (37) | 137 (46) | 0.100 |
| Interval to cognitive impairment (total) [years] | 8 ± 5 | 7 ± 3 | 8 ± 5 | 8 ± 5 | 0.353 |
| Development of cognitive impairment during observation period, n (%)[a] | 19 (43) | 1 (50) | 20 (44) | 43 (38) | 0.592 |
| Interval to cognitive impairment (conversion during observation period) [years][a] | 8 ± 3 | 7 ± 0 | 8 ± 3 | 8 ± 4 | 0.601 |

Abbreviations: *APOE,* Apolipoprotein; CSF, Cerebrospinal fluid; H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale part 3.

N=16 (4%) with missing *APOE* status; The p-value refers to group comparison of no *APOE* ε4 allele versus at least one *APOE* ε4 allele. [a] n=65 developed cognitive impairment during observation period, two with missing *APOE* status.

## Figures

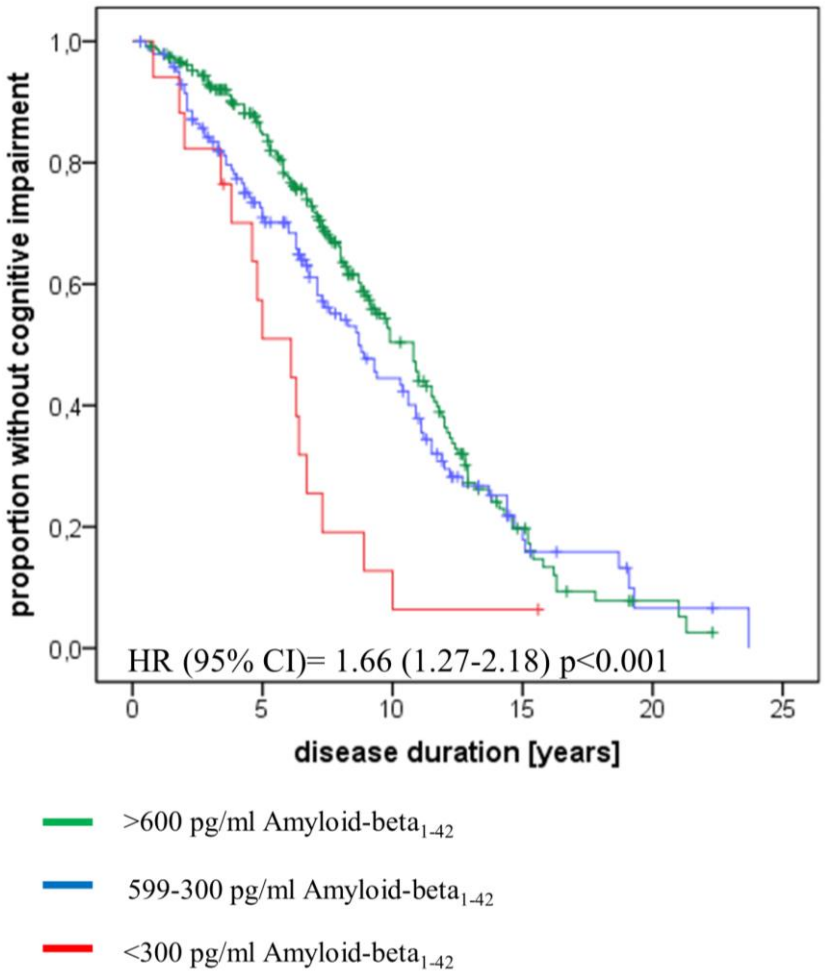
**Figure 1: Evolution of CSF Abeta$_{1-42}$ levels in healthy controls and PD patients stratified by cognitive status over 8 years**




Lines represent median values over time. **A)** All available CSF time points of PD patients and healthy controls **B)** CSF time points of all healthy controls and PD patients of whom CSF was available at baseline, six and eight year follow-up.

The black line represents PD patients who developed cognitive impairment during observation period with CSF Abeta$_{1_42}$ levels at last clinical visit free from cognitive impairment and at timepoint of conversion.

**Figure 2: Kaplan-Meier survival curves show the association between baseline CSF Abeta subgroups (low vs. mediate vs. high) and the risk of developing cognitive impairment**




Kaplan-Meier curves show disease duration free from cognitive impairment in PD patients classified by their baseline CSF $Abeta_{1-42}$ levels. The graphs demonstrate data with respect to disease duration (defined as the time from disease diagnosis until first clinical diagnosis of cognitive impairment). Hazard ratios (HR) with 95% confidence intervals (95% CI) and p-values from univariate Cox proportional hazard models with high $Abeta_{1-42}$ subgroup adopted as reference group.