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Cognitive Profile in Parkinson's Disease Dementia Patients with Low versus Normal Cerebrospinal Fluid Amyloid Beta

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Keywords
Parkinson's disease dementia · Cerebrospinal fluid · Amyloid beta · Cognitive assessment

Abstract
Introduction: In patients with Parkinson's disease (PD), low cerebrospinal fluid (CSF) amyloid beta 1-42 (Ab42) at baseline is the most consistent CSF biomarker as a risk factor for developing dementia. Low CSF Ab42 is, however, a typical hallmark of Alzheimer's disease (AD). Hence, low CSF Ab42 in patients with PD may indicate presence of comorbid AD pathology and may predict a more AD-like cognitive profile when they develop dementia. Our study aimed to investigate if low CSF Ab42 at baseline is associated with a more AD-like cognitive profile in PD patients with dementia. ***Methods:*** In a prospectively followed-up, population-based cohort of newly diagnosed PD patients, we compared the cognitive profile of dementia in those with a low CSF Ab42 level at baseline with that of patients who had normal levels at the time when they developed dementia. Four different cognitive domain z-scores (memory, attention, executive, visuospatial) were calculated. Patients were subdivided into three tertiles or categorized dichotomously based on the baseline CSF Ab42 levels as measured by electrochemiluminescence and ELISA. ***Results:*** During 10-year follow-up, 37 patients met the inclusion criteria. Memory domain composite z-scores, memory subtest z-scores, and the difference between long-delay free recall versus recognition scores were not significantly different between the groups. Composite z-scores of visuospatial functions significantly differed between the tertiles, which was not significant after Bonferroni correction. In the dichotomous group analysis, z-scores of visuospatial functions significantly differed between the two groups. The other cognitive domain z-scores were not significantly different. ***Conclusions:*** In patients with PD dementia, low CSF Ab42 level at baseline is not associated with a specific cognitive profile.

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Introduction

Cognitive impairment and dementia are among the most disabling non-motor symptoms of Parkinson's disease (PD). The point prevalence of dementia was found to be 24–31% in a systematic review; in the prospectively followed-up Sydney PD cohort, 48% of surviving patients had developed dementia 15 years after the diagnosis [1, 2].

The time of onset, severity, and the profile of cognitive impairment vary across patients. Several risk factors have been identified, with old age and severe motor symptoms being the most significant. A paradigm has been proposed to predict the risk of dementia [3]. In addition to clinical and demographic variables, low cerebrospinal fluid (CSF) amyloid beta 1-42 (Ab42) at baseline has been reported to be the most consistent biological risk factor for developing dementia [4–6]. On the other hand, low CSF Ab42 level is a typical hallmark of Alzheimer's disease (AD) along with high total tau and phospho-tau levels. We reasoned that in patients with PD, the presence of low CSF Ab42 at baseline may indicate the presence or predominance of AD-type pathology which may lead to a more AD-like cognitive profile when they develop dementia as compared to a more PD-like cognitive profile in those patients with normal CSF Ab42 at baseline. Therefore, we aimed to investigate whether patients with low versus those with normal CSF Ab42 level at baseline have different profiles of cognitive impairment when they develop dementia. Specifically, we tested the hypothesis if low CSF Ab42 at baseline would indicate a more AD-type cognitive profile with primary memory encoding deficits as opposed to a PD-like cognitive profile with predominantly executive function and visual-spatial deficits in those with normal CSF Ab42.

Methods

Subjects

Patients were recruited from the Norwegian ParkWest study, which is an ongoing population-based, multicenter, long-term cohort study of initially drug-naive, non-demented, newly diagnosed PD patients [7]. In this study, we used the data of the first 10 years of follow-up. Diagnostic procedures for PD and entry criteria for ParkWest have been described elsewhere [5, 7]. Patients who had baseline CSF biomarker values and a detailed clinical/neuropsychological evaluation, at least one post-baseline neuropsychological assessment, and developed dementia during the follow-up period were included in this study. Patients who developed dementia within 1 year of onset of motor symptoms were not included in order to exclude patients who would fulfill clinical criteria for dementia with Lewy bodies.

Diagnosis of PD Dementia

Diagnosis of dementia was based on the Movement Disorders Society criteria for clinical diagnosis of dementia associated with PD [8]. Patients with impairment in at least two cognitive domains and functional impairment in daily living activities due to cognitive impairment were diagnosed as having Parkinson's disease dementia (PDD).

CSF Analysis

Lumbar puncture was performed with standard procedures to obtain CSF at study entry, within 24 h of clinical and neuropsychological examinations [9]. Samples were frozen in polypropylene tubes at −80°C and subjected to one freeze-thaw event for aliquotation purposes. CSF concentrations of Ab42 were quantified at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, by electrochemiluminescence (ECL) using an Ab triplex assay (human Ab peptide Ultra-Sensitive Kit, Meso Scale Discovery, Gaithersburg, MD, USA). In addition, Ab42 was also analyzed using a sandwich ELISA method (Innotest b-amyloid [1-42]) at the Neuroscience Research Laboratory, Stavanger University Hospital, Stavanger, Norway [9].

Clinical and Neuropsychological Assessments

All patients underwent a neurological and neuropsychological assessment at study entry. They were examined by neurologists and trained research nurses experienced in movement disorders and cognitive assessment. Neurological examination was performed at baseline and at 6-month intervals thereafter, and neuropsychological assessment was performed at the 1st, 3rd, 5th, 7th, 9th, and 10th years during follow-up.

The severity of motor symptoms was determined using the Unified Parkinson's Disease Rating Scale (UPDRS) part III, motor subscale [10]. Mean scores for tremor, rigidity, bradykinesia, and axial impairment were obtained to assess the pattern of parkinsonism, as described previously [11]. An extensive neuropsychological test (NPT) battery was used to assess cognitive subdomains, including California Verbal Learning Test II (CVLT-II) [12] for verbal memory, Stroop test and semantic verbal fluency (animals) for executive functions and attention [13], Visual Object and Space Perception (VOSP) battery silhouettes and cube subtests [14] for visuospatial functions.

Neuropsychological test results obtained at the visit, at which the patient was diagnosed to have developed dementia, were used in the analyses. The test results obtained at the closest visit were used if the neuropsychological assessment was not performed at the visit at which dementia was clinically diagnosed.

Domain-Specific Composite Z-Scores

Four different cognitive domain scores were calculated. Total immediate recall (sum of trials 1–5), short-delay free recall, and long-delay free recall (after 20 min) scores of CVLT-II were used to calculate the memory domain score. Stroop test interference (part 3) and semantic verbal fluency (animals) test scores were used to calculate the executive domain score. Stroop test word reading (part 1) and color reading (part 2) scores constituted the components of the attention domain. Visual Object and Space Perception (VOSP) battery silhouettes and cube subtest scores were used to calculate the visuospatial domain score. The raw scores for each test were converted to age- and education-corrected z-scores,

as described before [15]. Finally, composite z-scores were computed by dividing the sum of individual adjusted z-scores of tests included in each domain by the number of tests as shown below:

$$\text{Memory z-score} = (\text{CVLT-II total immediate recall z-score}) + \frac{(\text{short-delay recall z-score}) + (\text{long-delay free recall z-score})}{3}$$

$$\text{Attention z-score} = \frac{(\text{Stroop words z-score}) + (\text{Stroop colors z-score})}{2}$$

$$\text{Executive z-score} = \frac{(\text{Stroop interference z-score}) + (\text{Semantic verbal fluency z-score})}{2}$$

$$\text{Visuospatial z-score} = \frac{(\text{VOSP silhouettes z-score}) + (\text{VOSP cube z-score})}{2}$$

We also calculated the difference between long-delay free recall and recognition scores. Lower mean difference between free recall and recognition raw scores would indicate no benefit from cuing and suggest a memory storage failure compatible with primary amnestic type memory impairment, whereas a higher difference would indicate benefit from cuing compatible with a secondary type memory impairment with relative sparing of memory storage.

Changes in Cognitive Domain Z-Scores from Baseline

Changes from baseline to time of PDD diagnosis in each cognitive domain z-score were calculated as the absolute value of the difference between each cognitive domain z-score at baseline and at the time of PDD diagnosis for each patient.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (#2010/1700). Signed written informed consent was obtained from all participants.

Statistical Analyses

Statistical analyses were performed using the SPSS software version 25. The variables were tested for normality using visual and analytical methods (Shapiro-Wilk's test). Descriptive statistics were presented using medians and tertiles for non-normally distributed and ordinal variables as well as means and standard deviations for normally distributed variables. Parametric tests were performed for normally distributed variables, and non-parametric tests were used for ordinal and non-normally distributed variables. Due to non-normal distribution, the strengths of correlations were expressed as Spearman correlation coefficients. Differences in continuous clinical and demographic variables were analyzed using the Mann-Whitney U test and Kruskal-Wallis tests. Bonferroni correction was used to adjust for multiple comparisons.

Patients were subdivided into three tertiles based on the baseline value of CSF Ab42 levels as measured by ECL and ELISA. They were also categorized dichotomously based on the baseline median CSF Ab42 levels for each measurement method. Cognitive domain z-scores were compared between these tertiles and dichotomous groups. We also compared the difference between long-delay free recall and recognition scores across the groups. p values <0.05 were considered significant.

Results

During 10 years of follow-up, 67 out of 190 patients developed dementia, 38 of these had baseline CSF Ab42 values. Of these, all had at least one post-baseline neuropsychological assessment, except 1 patient who was unable to comply with test procedures. The remaining 37 patients were entered in the analysis. Demographic and clinical characteristics are summarized in Table 1. They were predominantly male (89%), mean age was 70 years, and mean duration of formal education was 10.6 years.

The mean duration from baseline to the time of dementia diagnosis was 6.1 (2.0–10.0) years. The mean baseline CSF concentration of Ab42 was 402.27 pg/mL measured by ELISA and 280 pg/mL measured by ECL. Amyloid beta 42 concentrations measured by ELISA and ECL were highly correlated (r_S: 0.62, $p < 0.001$).

Memory domain composite z-scores at the time of dementia diagnosis were not significantly different between the tertiles or dichotomous groups based on the baseline Ab42 levels measured by ECL or ELISA (Table 2). Similarly, memory subtest z-scores did not significantly differ between tertile groups or dichotomous groups (Table 3). Composite z-scores of visuospatial functions significantly differed between the three tertile groups, but this difference was not significant after Bonferroni correction ($p > 0.017$) (Table 2). In the dichotomous group analysis based on ELISA measurements, z-scores of visuospatial functions significantly differed between the two groups (Table 2). The other cognitive domain z-scores were not significantly different.

Long-delay free recall z-scores of CVLT-II memory test did not significantly differ between the three tertiles or dichotomous groups (Table 3). Likewise, the difference between the recognition score and long-delay free recall score did not significantly differ between the tertiles or dichotomous groups, and a lower difference between the two measures did not correlate with lower baseline CSF Ab42 levels (Table 4), indicating that all groups had a comparable benefit from cuing.

We also analyzed correlations between different cognitive domains at baseline, correlations at the time of dementia diagnosis, and correlations between changes from baseline to time of dementia across cognitive

Table 1. Demographic and clinical characteristics of PDD patients

N: 37	
Age, years, mean	70.1±6.2 (59.5–83.4)
Male, *n* (%)	33 (89.2)
Education, years, mean	10.6±2.8 (7–18)
UPDRS part II score, mean	8.9±4.5 (1–17)
UPDRS part III score, mean	23.7±10.7 (8–52)
Age at motor symptoms onset, years, mean	67.7±6.2 (53.1–81.4)
Type of PD, *n* (%)	
PIGD	14 (37.8)
Indeterminate	2 (5.4)
Tremor dominant	21 (56.8)
Age at PDD onset, years, mean	76.2±5.3 (66.6–87.0)
Time to PDD from baseline, years, mean	6.1±2.4 (2.0–10.0)
Baseline CSF Ab42 ECL, pg/mL, median	280.0 (106.0–841.0)
Baseline CSF Ab42 ELISA, pg/mL, median	402.3 (181.7–1,031.6)

CSF, cerebrospinal fluid; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; PDD, Parkinson's disease dementia; PIGD, postural instability and gait difficulty; UPDRS, Unified Parkinson's Disease Rating Scale.

domains. At baseline attention, executive and visuospatial domain z-scores correlated with each other. Likewise at the time of PDD diagnosis, these three domains correlated with each other but not with memory. At the time of PDD diagnosis, baseline memory z-scores correlated with memory z-score; baseline attention z-scores correlated with memory z-scores; baseline executive z-scores correlated with executive and attention z-scores; baseline visuospatial z-scores correlated with visuospatial z-scores. Thus, each cognitive domain z-score at baseline correlated with the same cognitive domain z-score at the time of PDD except baseline attention domain. At the time of dementia, diagnosis executive and attention, visuospatial and attention, executive and visuospatial domain z-scores correlated with each other but not with memory domain z-scores (Fig. 1). There were no correlations between the change in z-score of memory domain with changes in z-scores of other domains. The change in executive domain z-score was correlated with change in visuospatial domain z-score and change in attention domain z-score.

Discussion

In patients with PD, a low CSF Ab42 level at baseline is the most consistent biomarker as a risk factor for developing dementia. As low CSF Ab42 level is a biological hallmark of AD, we hypothesized that this may indicate the presence or predominance of comorbid AD pathology and predict a more AD-like cognitive profile with more prominent memory impairment in PD patients with low CSF Ab42 levels at baseline, as opposed to a more PD-like cognitive profile with more prominent executive function and visual-spatial impairment in those with normal Ab42 levels. Our results did not demonstrate such an association.

Although cognitive impairment may accompany motor impairment at the onset of the disease, majority of patients remain cognitively intact for many years [16]. A number of risk factors have been described for development of cognitive impairment and dementia in PD. These include neuropsychological and MRI changes associated with posterior-cortical involvement, amnestic mild cognitive impairment, longer disease duration, older age at onset, severity of motor symptoms, male gender, glucocerebrosidase status, caudate nucleus involvement in DatScan, REM sleep behavior disorder, and electroencephalographic slowing during REM sleep [3, 17–22]. Some of these risk factors have not been replicated. Low CSF Ab42 values at baseline, however, have been consistently reported to be associated with risk for dementia in several prospective studies [4–6, 23]. In addition, clinicopathological studies revealed that the presence of amyloid beta may indicate worse cognitive functions [24, 25].

The presence of low CSF Ab42 is considered to reflect aggregation and deposition of amyloid in the brain, which is a hallmark of AD pathology. Pathologically, amyloid deposition is also seen in a subgroup of PD patients, especially in those with dementia, and up to

Table 2. Cognitive domain composite Z-scores based on baseline CSF Ab42 (pg/mL) levels as measured by ECL and ELISA

ECL, pg/mL	Memory z-score			Attention z-score			Executive z-score			Visuospatial z-score		
	N	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*
Tertiles based on baseline CSF Ab42			0.82			0.52			0.73			**0.02**
106.00–201.33	9	−1.5±0.7		12	−2.5±1.0		11	−2.2±0.9		12	−4.4±2.8	
201.33–367.67	12	−1.4±0.7		13	−2.3±1.0		12	−1.9±0.9		13	−2.4±3.8	
367.67–841	12	−1.7±0.7		11	−2.6±1.2		11	−2.2±1.0		11	−7.8±5.0	
	N	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			1.0			0.67			0.84			0.21
106.00–280.00	16	−1.6±0.6		19	−2.4±1.0		18	−2.1±0.9		19	−3.5±3.0	
281.00–841	17	−1.5±0.7		17	−2.5±1.2		16	−2.1±1.0		17	−6.0±5.4	
ELISA, pg/mL	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*
Tertiles based on baseline CSF Ab42			0.08			0.60			0.36			0.24
181.66–350.56	10	−1.5±0.6		12	−2.2±1.1		11	−1.8±1.0		12	−3.9±2.7	
350.56–459.32	12	−1.2±0.8		13	−2.4±1.1		12	−2.0±1.0		13	−3.5±4.2	
459.32–1,031.64	11	−1.9±0.5		11	−2.8±1.0		11	−2.4±0.7		11	−7.0±5.6	
	N	mean±SD	*p* value#	N	mean±SD	*p* value#	N	mean±SD	*p* value#	N	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			0.49			0.09			0.20			**0.05**
181.66–402.27	17	−1.5±0.7		19	−2.1±1.0		18	−1.9±0.9		19	−3.1±3.2	
402.28–1,031.64	16	−1.7±0.6		17	−2.8±1.1		16	−2.3±0.9		17	−6.5±5.0	

CSF, cerebrospinal fluid; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay. *Kruskal-Wallis test. #Mann-Whitney U test.

half of those PDD patients with amyloid plaques also had concomitant neurofibrillary tangles sufficient for the diagnosis of AD [26]. This observation, however, is not corroborated by amyloid imaging with PET, which indicates that only a small percentage of patients with PDD have significant amyloid accumulation in the brain [27, 28]. In one study, the incidence of amyloid positivity in PD patients with normal cognition was similar to those with PD-MCI lower than that in healthy controls and PDD patients [28]. Based on these conflicting findings, the relevance of AD pathology and its contribution to clinical symptoms in PDD is not well established. It has been suggested that amyloid beta may not be a primary driver but rather represent a comorbid pathology [25, 29].

The profile of cognitive impairment in patients with PD-MCI or PDD is different than that seen in patients with AD dementia. In the early stages of the disease, the majority of cognitively impaired PD patients have multi-domain cognitive impairment as opposed to primary amnestic-type memory impairment in patients with early-stage AD [30]. The dual syndrome hypothesis proposed that dysfunction in two separate networks may underlie this multi-domain impairment [31]. The fronto-striatal network modulated by dopamine may cause deficits in attention/working memory and executive functions, while posterior-cortical involvement with cholinergic loss may be associated with predominantly memory, language, and visuospatial impairment, more prone to progress to dementia. In patients with dementia, those with AD have more prominent memory impairment, whereas those with PDD have more prominent impairment in memory and executive functions.

In a study of non-demented, early-stage PD patients, low CSF Ab42 levels were associated with more

Table 3. Memory domain composite z-scores in tertiles and dichotomous groups based on baseline CSF Ab42 (pg/mL) levels as measured by ECL and ELISA

ECL, pg/mL	CVLT-II total immediate recall z-score			CVLT-II short-delay recall z-score			CVLT-II long-delay free recall z-score			CVLT-II forced choice recognition z-score		
	N	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*
Tertiles based on baseline CSF Ab42			0.31			0.64			0.67			0.15
106.00–201.33	10	−1.6±0.4		9	−1.9±0.5		9	−1.9±0.6		10	−2.8±3.5	
201.33–367.67	12	−1.6±0.7		12	−1.8±0.7		12	−2.0±0.7		12	0.0±2.9	
367.67–841	12	−2.0±0.5		12	−2.0±0.6		12	−1.9±0.7		12	−2.5±4.2	
	N	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			0.99			0.63			0.69			0.99
106.00–280.00	16	−1.7±0.6		16	−1.8±0.6		16	−2.0±0.6		17	−1.4±3.7	
281.00–841	17	−1.8±0.6		17	−1.9±0.6		17	−1.9±0.7		17	−2.0±3.7	
ELISA, pg/mL	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*	*N*	mean±SD	*p* value*
Tertiles based on baseline CSF Ab42			0.29			0.09			0.43			0.98
181.66–350.56	10	−1.7±0.5		10	−1.8±0.6		10	−1.9±0.7		11	−1.8±3.1	
350.56–459.32	12	−1.6±0.7		12	−1.7±0.7		12	−1.8±0.8		12	−1.6±4.9	
459.32–1,031.64	11	−1.9±0.5		11	−2.2±0.3		11	−2.2±0.5		11	−1.6±3.0	
	N	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#	*N*	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			0.62			0.48			0.97			0.90
181.66–402.27	17	−1.8±0.6		17	−1.8±0.6		17	−2.0±0.7		18	−1.8±4.5	
402.28–1,031.64	16	−1.7±0.5		16	−2.0±0.6		16	−1.9±0.7		16	−1.5±4.7	

CSF, cerebrospinal fluid; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay. *Kruskal-Wallis test. #Mann-Whitney U test.

prominent memory impairment, the subsequent cognitive profile of these patients when they progressed to dementia, however, was not studied [9, 32]. One of the main purposes of this study was to investigate whether a low CSF Ab42 level at baseline indicates an "Alzheimerization" of the pathology and would predict a more AD-type cognitive profile with primary memory impairment. There have been several cross-sectional or longitudinal studies with a short follow-up time which assessed the cognitive profiles of PDD or PD-MCI patients based on their amyloid beta status evaluated by CSF or PET images. The results were not consistent. In a cross-sectional study with PD patients having normal cognition, mild cognitive impairment, or dementia, Melzer et al. [29] did not find an association between amyloid PET binding status and global cognitive or memory scores. Palermo et al. [33] found that 52% of 21 PDD patients were amyloid positive based on a semi-quantitative PET assessment method, and these patients had more severe memory impairment and a faster rate of cognitive decline. In another cross-sectional study, cortical amyloid binding was positive in 15% of PD-MCI patients, and there was a correlation between global cognitive functions and Pittsburgh compound B positron emission tomography positivity [34]. Garon et al. [35], however, did not find a difference in global cognitive performance between amyloid PET positive and negative PD-MCI patients, whereas executive functions were worse in amyloid-positive group. Biundo et al. [36] found worse performance in global function tests as well

Table 4. CVLT-II forced choice recognition raw score minus long-delay free recall raw score in tertiles and dichotomotus groups based on baseline CSF Ab42 levels (pg/mL) as measured by ECL and ELISA

ECL, pg/mL	(CVLT-II forced choice recognition raw score) minus (CVLT-II long-delay free recall raw score)		
	N	mean ± SD	*p* value*
Tertiles based on baseline CSF Ab42			0.62
106.00–201.33	9	12.3±2.1	
201.33–367.67	11	13.2±2.2	
367.67–841	12	12.4±2.6	
	N	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			0.61
106.00–280.00	15	12.9±2.2	
281.00–841	17	12.5±2.5	
ELISA, pg/mL	*N*	mean±SD	*p* value*
Tertiles based on baseline CSF Ab42			0.12
181.66–350.56	10	12.9±2.5	
350.56–459.32	11	11.6±2.1	
459.32–1,031.64	11	13.6±2.2	
	N	mean±SD	*p* value#
Dichotomous groups based on median of baseline CSF Ab42			0.75
181.66–402.27	16	12.5±2.4	
402.28–1,031.64	16	12.8±2.3	

CSF, cerebrospinal fluid; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay. *Kruskal-Wallis test. #Mann-Whitney U test.

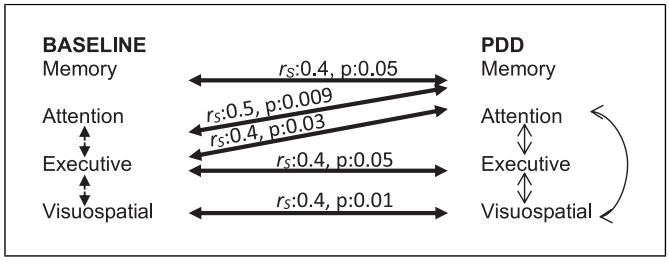

Fig. 1. Correlations between cognitive domain z-scores at baseline (dotted arrows), at the time of the PDD diagnosis (thin arrows), and between baseline and at the time of PDD diagnosis (bold arrows).

as in executive and language functions at baseline in amyloid-positive PD patients, and they were more prone to develop dementia after 1-year follow-up period. They did not describe the cognitive profile of patients when they developed dementia.

In our study, there were no statistically significant differences in most cognitive domains between demented PD patients with low versus normal baseline CSF Ab42 levels, except for visuospatial domain. In particular, low baseline CSF Ab42 levels did not predict a more prominent primary amnestic (AD-type) memory impairment at the time of PDD diagnosis. As such, our findings suggest that coexistent amyloid pathology does not significantly determine the clinical profile of dementia in patients with PDD. This may imply that amyloid may have a different pathophysiological role in patients with PD such as induction of or interaction with alpha-synuclein pathology.

Our results need confirmation. The prospective cohort study design, long follow-up period, comprehensive annual neurological and cognitive assessments, two different measurement methods for detecting CSF Ab42 levels, and two different categorizations of patients according to baseline CSF Ab42 levels are the main strengths of this study. The relatively small number of patients who developed dementia and for whom baseline CSF Ab42 levels were available constitute the main limitations of our study.

Cutoff values of CSF Ab42 levels for biological diagnosis of AD have also been successively modified. Further prospective studies in larger de novo PD populations with assessment of CSF and plasma Ab42 and other biomarkers combined with amyloid imaging and detailed neuropsychological assessments are required to better elucidate the contribution of amyloid pathology to the cognitive profile of patients with PDD.

Statement of Ethics

The study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (#2010/1700). Signed written informed consent was obtained from all participants.

Conflict of Interest Statement

None of the authors had any disclosures relevant to the research covered in this study.

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Author Contributions

Z.T. and M.E.: design, execution, analysis, writing, and editing of the final version of the manuscript; J.L., K.F.P., and G.A.: design, execution, and editing of the final version of the manuscript; and O.-B.T.: execution and editing of the final version of the manuscript.

Data Availability Statement

Anonymized data that support the findings of this study are available on request and with the correct permissions from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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