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CSF A β LEVELS CORRELATE WITH STRUCTURAL BRAIN CHANGES IN PARKINSON'S DISEASE

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Abstract

Background—ParkWest is a large Norwegian multicenter study of newly diagnosed drug-naïve subjects with Parkinson's disease (PD). Cognitively normal PD subjects (PDCN) and PD subjects with mild cognitive impairment (PDMCI) from this cohort have significant hippocampal atrophy and ventricular enlargement compared to normal controls. Here we aimed to investigate whether the same structural changes are associated with CSF levels of A β ₃₈, A β ₄₀, A β ₄₂, total tau and phosphorylated tau.

Methods—We performed 3D radial distance analyses of the hippocampi and lateral ventricles using the MRI data from ParkWest subjects who provided CSF at baseline. Our sample consisted of 73 PDCN and 18 PDMCI subjects.

Results—We found significant associations between the levels of all three CSF A β analytes and t-tau and lateral ventricular enlargement in the pooled sample. In the PDCN sample all three amyloid analytes showed significant associations with the radial distance of the occipital and frontal horns of the lateral ventricles. CSF A β ₃₈ and A β ₄₂ showed negative associations with enlargement in occipital and frontal horns of the lateral ventricles in the pooled sample, and a negative association with the occipital horns in PDMCI.

Conclusion—CSF A β levels in early PD correlate with ventricular enlargement, previously associated with PDD. CSF and MRI markers may therefore help identify PD patients at high risk for developing cognitive decline and dementia in the course of their illness. Contrary to Alzheimer's disease, we found no associations between CSF t-tau and p-tau and hippocampal atrophy.

Keywords

Parkinson disease; Mild Cognitive Impairment; Magnetic Resonance Imaging; Cerebrospinal Fluid; Hippocampus; Lateral Ventricles

1. Introduction

Mild cognitive impairment (MCI) is often present in Parkinson's disease (PD) patients at the time of diagnosis¹. PD subjects with MCI (PDMCI) are about five times more likely to receive a diagnosis of dementia over the following four years.² Pathologically, PD is characterized by progressive degeneration of dopaminergic neurons, Lewy bodies and Lewy neurites. Cortical Lewy bodies are characteristic for PD dementia (PDD)³. Diffuse cortical amyloid deposition has been reported post-mortem in PDD⁴ suggesting that the interface between PD and Alzheimer's disease (AD) needs to be more thoroughly investigated. Co-existing AD pathology promotes more rapid cognitive decline and early dementia in PD⁵.

Amyloid beta 1-42 (A β ₄₂), total tau (t-tau) and phosphorylated tau (p-tau) are the most established cerebrospinal fluid (CSF) biomarkers of AD. Low CSF A β ₄₂ and high CSF t-tau and p-tau levels have been reported in AD and in MCI subjects who later converted to AD⁶. Investigations into the levels of traditional CSF AD biomarkers in PD have been conflicting^{7, 8, 9}. Yet recent large-scale studies have reported reduced CSF levels of A β ₄₂ in both cognitively normal and cognitively impaired PD patients^{10, 11}. We recently reported reduced CSF A β ₄₂, but normal CSF t-tau and p-tau levels in our newly diagnosed drug-naïve ParkWest PD cohort¹⁰.

CSF A β ₄₂, t-tau and p-tau levels have been linked to hippocampal atrophy and ventricular enlargement in AD^{12, 13, 14}. Ventricular enlargement, hippocampal atrophy and white matter

hyperintensities (WMH) are commonly seen in PD and have been associated with cognitive decline^{15, 16, 17, 18}. Previous ParkWest analyses showed larger ventricles but no hippocampal atrophy or greater WMH burden in PDMCI relative to PDCN^{15,19}. The associations between white matter changes and CSF markers in the ParkWest sample is currently being investigated. A previously published ParkWest analysis failed to find an association between WMH and cognitive performance¹⁹. However, as other research groups have reported potential associations between cognitive function and CSF markers in PD²⁰ and that white matter change may contribute to cognitive deficits associated with PD¹⁶, we have included WMH as a covariate in our analyses.

Whether CSF A β and tau markers are associated with ventricular enlargement and hippocampal atrophy in PD remains to be determined. The aim of this study was to investigate in a 3 dimensional (3D) model whether these MRI measures are associated with CSF levels of A β ₃₈, A β ₄₀, A β ₄₂, t-tau and p-tau in early, untreated PD patients with and without MCI.

2. Methods

2.1 Subjects

All subjects are participants of the ongoing Norwegian ParkWest study²¹. ParkWest - a population-based multi-center prospective longitudinal cohort study- aiming to improve our understanding of motor and non-motor PD progression and to develop promising biomarkers for PDMCI and PDD. Only newly diagnosed drug-naïve PD subjects meeting the Gelb clinical criteria for PD²² were eligible to participate.

Diagnostic procedures included evaluation of medical history, standardized clinical, neuropsychiatric and neuropsychological examinations at study entry, radiological examination with 3-dimensional T1-weighted brain magnetic resonance imaging (MRI), dopamine transporter imaging when available (n=31), and repeated clinical assessments to evaluate drug response. Patients with atypical parkinsonism or dementia during the first year of motor onset were excluded, according to the revised DLB criteria by McKeith IG et al.²³ The details of the diagnostic ascertainment are reported in Alves et al, 2009²⁴.

Of the 207 drug-naïve incident PD subjects who agreed to longitudinal participation, 91 provided CSF and MRI data at baseline. Seventy-three were cognitively intact (PDCN) while 18 met criteria for PDMCI. All participants signed informed consent. The study protocol was approved by the Regional Committee for Medical Research Ethics, Western Norway.

2.2 Clinical and neuropsychological examination

Severity of parkinsonian symptoms was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS)²⁵ and the modified Hoehn and Yahr (H&Y) scale²⁶. All PD subjects underwent neuropsychological assessments of memory, executive and visuospatial function²¹, which consisted of the Mini-Mental State Examination scale (MMSE)²⁷, verbal memory assessment with the California Verbal Learning Test II²⁸, visuospatial assessment with the Silhouettes and Cube subtests from the Visual Object and the Space Perception Battery²⁹ and assessment of attention and executive functioning with a semantic verbal fluency test (animal fluency)³⁰, the serial 7 test from the MMSE²⁷ and the Stroop test³¹.

Cognitive data for all PD subjects were converted to z-scores using the mean and standard deviations of an age-matched cognitively intact control group as previously described^{21,15}. PD subjects with cognitive performance more than 1.5 standard deviations below the

predicted by an age-, education-, and sex-corrected linear regression model in one or more cognitive domains were classified as having PDMCI.

2.3 Magnetic resonance imaging (MRI)

MRI was performed at four of the five study sites. 1.5 Tesla MRI scanner was used at three centers (Philips Intera, Best, The Netherlands at Stavanger and Haugesund, and Siemens Symphony, Erlangen, Germany, in Bergen). 1.0 Tesla Philips Intera system, (Best, The Netherlands) was used at Arendal.

The following protocols were used:

- Stavanger: TR/TE 10.0/4.6 msec, flip angle 30.0 degrees, 1 mm slices with no gap, NEX 2, Matrix 256×256
- Haugesund: TR/TE 20.0/4.6msec, flip angle 30.0 degrees, 1 mm slice thickness with no gap, NEX 1, Matrix 256×256
- Bergen: TR/TE 2130.0/3.9msec, flip angle 15.0 degrees, 1 mm slice thickness with no gap, NEX 1, Matrix 256×256
- Arendal: TR/TE 25/6.9msec, flip angle 30.0 degrees, 2 mm slice thickness with no gap, NEX 1, Matrix 256×256.

All baseline images were inspected by two neuroradiologists. Scans with large vessel cortical infarcts or other structural lesions that could result in parkinsonian symptoms (N=7) were excluded. 12 subjects with scan or movement artifacts and 5 subjects with baseline dementia were also excluded from the study.

2.4 Imaging analyses

The 3D T1-weighted MRI data were subjected to intensity³² and spatial normalization to the International Consortium for Brain Mapping ICBM53 brain atlas using a 9-parameter transformation (3 translations, 3 rotations, 3 scales)³³. The hippocampal formations of a randomly selected ParkWest training data set were manually segmented on gapless coronal slices by one experienced rater (MKB) blinded to subjects' age, sex, and diagnosis following a detailed, well-established protocol. The traces were closely inspected for accuracy by a second experienced hippocampal rater (LGA). The training sample composition was proportionate to the ratio of subject enrolment across the four imaging centers, to prevent as far as possible potential center bias in the statistical sampling. The hippocampal traces included hippocampus proper, dentate gyrus and subiculum.

2.4.1 Hippocampal segmentation—The hippocampi of the full dataset were segmented with our automated machine-learning hippocampal segmentation approach, based on statistical adaptive boosting³⁴. Using the manually traced hippocampal training set, AdaBoost develops statistical rules for classifying each voxel in a new image as belonging to the hippocampus or not. Based on the feature information contained in the positive and negative voxels of the training dataset, AdaBoost developed a set of rules and computed the optimal combination and weighting of these features for accurate segmentation of unknown images³⁴.

2.4.2 Ventricular segmentation—We employed a previously validated semi-automated ventricular segmentation approach (MAFIA)³⁵. Briefly, a human rater (MKB) first traced the lateral ventricles of four subjects. These traces were converted into 3D parametric ventricular mesh models, termed atlases. Using fluid registration, each atlas was separately warped to match and thereby extract the shape of the lateral ventricle of each new subject's

scan. This resulted in four lateral ventricle segmentations per subject, which were then averaged to create one final ventricular model. Averaging four separate segmentations minimizes automated labeling errors that occur when only one atlas is used.

After converting the segmented hippocampi and lateral ventricles into 3D parametric meshes, we computed the medial core (a medial curve threading down the center of each structure) and the radial distance from the medial core to each surface point for each structure in each subject³⁶. Radial distance provides an intuitive measure of the thickness of the structure from its core to each point on its boundary.

Analysis of white matter hyperintense lesion volumes:

Mask of white matter hyperintense lesions (WMH) were prepared using a semiautomated local threshold technique on axial FLAIR images as previously described¹⁹. One single rater created the masks blinded to diagnosis and test results, with excellent reproducibility. Normalized volumes of WMH (to total brain volume) were used in the further analyses.

2.4.3 Inter-Scanner Reliability Analyses—In order to test scanner reliability we conducted human phantom scanning. Three cognitively normal volunteers were imaged twice on the same day on each scanner. The hippocampi were manually traced and volumes obtained as previously described. Whole brain volumes were obtained using Sienax³⁷. We used PASW software (PASW for Windows Release 18.0.1) to obtain Cronbach's Alpha reliability coefficients on whole brain and hippocampal volumetric measurements between scanning sites. Inter-site Cronbach's Alpha for whole brain volume was 0.96 and for hippocampal volume was 0.97.

2.5 CSF collection and analyses

All lumbar punctures were performed between 7 and 10 am after overnight fast in order to minimize diurnal variation of the level of CSF A β . CSF levels of A β ₃₈, A β ₄₀ and A β ₄₂ were quantified by an A β triplex assay (Human A β peptide Ultra-Sensitive Kit, Meso Scale Discovery, Gaithersburg, Maryland, USA). CSF levels of t-tau and p-tau were analyzed using a commercial sandwich ELISA (INNOTEST[®] hTAU-Ag and INNOTEST[®] PHOSPHO-TAU_(181P), Innogenetics, Gent, Belgium). CSF samples were randomized and run in duplicates, blinded for clinical diagnosis, according to the manufacturer's instructions.

2.6 Apolipoprotein E analysis

DNA was extracted from 200 μ l of EDTA-blood using the QIAamp 96 DNA Blood Kit (Qiagen, Hilden, Germany). Apolipoprotein E genotype was determined using the Light Cycler APOE Mutation Detection Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions.

2.7 Statistical methods

Demographic and clinical between-group comparisons were conducted with two-sample t-test using PASW software. Differences in sex and apolipoprotein E4 genotype (APOE4) distributions were assessed with a χ^2 test. The presence of at least one APOE4 allele was coded as 1, the absence was coded as 0. Three PDCN with missing APOE4 data were coded as 0.5. Variables with non-normal distribution (i.e., MMSE) were analyzed using the Mann-Whitney U test. We used univariate statistics to examine for an effect of age, APOE4, WMH and scanning site on CSF analytes and ventricular volume in our sample.

Main analyses were conducted with linear regression. The models tested the associations between hippocampal and ventricular radial distance (or volume) and CSF variables while adjusting for scanning site, age, WMH and APOE4. Partial correlations between ventricular volumes and CSF variables while adjusting for age, scanning site, WMH and APOE4 were also sought.

For 3D map-wise multiple comparisons correction, we ran 100,000 permutations thresholded at $p < 0.01$. After completion of these random permutations a final corrected p-value is computed indicating in what proportion of the iterations the experimental p-value beat the p-value of the original experiment.

3. Results

CSF A β , t-tau and p-tau were available for 91, 84 and 89 subjects respectively. There were no differences in age, education, motor subscale of UPDRS (UPDRSm) or H&Y, APOE4 genotype or MMSE between subjects who agreed or refused to undergo a lumbar puncture. A significantly greater proportion of men agreed to a lumbar puncture compared to women (68 % vs. 43%; $p = 0.015$).

PDMCI subjects were on average older and had lower mean MMSE score than PDCN. There were no significant differences in CSF analyte levels between the diagnostic groups or between APOE4 carriers and noncarriers (Table 1). PDMCI subjects had significantly larger left and trend larger right ventricular volumes (left $p = 0.027$, right $p = 0.083$) but comparable hippocampal volumes compared to PDCN (Table 1).

3D univariate age, center, APOE4 and WMH statistical maps are provided in Figure 1. Only age and WMH showed significant association with ventricular radial distance (age left $p_{\text{corrected}} = 0.04$, right $p_{\text{corrected}} = 0.0006$; WMH left $p_{\text{corrected}} = 0.045$, right $p_{\text{corrected}} = 0.053$). Age was also correlated with hippocampal volume (left $r = -0.17$, $p = 0.019$; right $r = -0.36$, $p < 0.001$), A β_{40} ($r = 0.25$, $p = 0.016$), t-tau ($r = 0.44$, $p < 0.001$) and p-tau ($r = 0.23$, $p = 0.03$). WMH volume was correlated with hippocampal volume (left $r = -0.38$, $p < 0.001$; right $r = -0.24$, $p = 0.03$) and t-tau ($r = 0.4$, $p < 0.001$). One-way ANOVA showed no significant differences in mean CSF analyte levels between centers.

It is worth noting that our results were not driven by outliers, that the regression standardized residuals had a normal distribution and that we excluded the possibility of multi-collinearity using the collinearity diagnostics option procedure recommended by Belsey and Kuh³⁸.

Multivariate analyses

3D regression analyses were conducted in the pooled sample and then separately in PDCN and PDMCI while controlling for age, APOE4 status, WMH and scanning site. We found no significant associations between any of our CSF analytes and hippocampal radial distance (maps not shown).

In contrast, we found significant associations with ventricular radial distance. In the pooled sample (Figure 2), all three amyloid measures showed significant negative associations with the occipital (A β_{38} : left $p_{\text{corrected}} = 0.0023$, right $p_{\text{corrected}} = 0.0034$; A β_{40} : left $p_{\text{corrected}} = 0.025$, right $p_{\text{corrected}} = 0.043$; A β_{42} : left $p_{\text{corrected}} = 0.022$, right $p_{\text{corrected}} = 0.01$) and frontal horns (A β_{38} : left $p_{\text{corrected}} = 0.0022$, right $p_{\text{corrected}} = 0.0027$; A β_{40} : left $p_{\text{corrected}} = 0.016$, right $p_{\text{corrected}} = 0.01$; A β_{42} : left $p_{\text{corrected}} = 0.0054$, right $p_{\text{corrected}} = 0.0045$). CSF t-tau showed significant negative associations with the left occipital ($p_{\text{corrected}} = 0.046$) and frontal horns ($p_{\text{corrected}} = 0.034$).

In PDMCI only $A\beta_{40}$ showed a trend level significant negative association with the right occipital horn enlargement (right $p_{\text{corrected}}=0.063$), (see Supplementary Figure 3).

In PDCN all three amyloid measures showed significant associations with the radial distance of the occipital and frontal horns of the lateral ventricles (occipital horn $A\beta_{38}$: left $p_{\text{corrected}}=0.01$, right $p_{\text{corrected}}=0.0088$, $A\beta_{40}$: left $p_{\text{corrected}}=0.07$, right $p_{\text{corrected}}=0.029$, $A\beta_{42}$: left $p_{\text{corrected}}=0.057$, right $p_{\text{corrected}}=0.046$; frontal horn $A\beta_{38}$: left $p_{\text{corrected}}=0.0027$, right $p_{\text{corrected}}=0.0033$, $A\beta_{40}$: left $p_{\text{corrected}}=0.059$, right $p_{\text{corrected}}=0.018$, $A\beta_{42}$: left $p_{\text{corrected}}=0.015$, right $p_{\text{corrected}}=0.0052$), (see Supplementary Figure 4). T-tau and p-tau showed no significant associations with the morphology of the lateral ventricles in PDCN.

We repeated the linear regression analyses with ventricular volumes as the dependent variable. In all cases the direction of the observed associations remained unchanged yet some of the effects became trend level or not significant (Supplementary Table 1). We also reversed the regression models taking CSF analytes as the dependent variables. Mean hippocampal volume was not a significant predictor of any CSF measure. Mean ventricular volume was significant predictor of CSF $A\beta_{38}$ ($p=0.03$), $A\beta_{40}$ ($p=0.016$) and $A\beta_{42}$ ($p=0.007$). Finally, we repeated the analyses after removing all subjects scanned on the 1T MRI instrument. The results remained largely unchanged (Supplementary Table 2, Supplementary Figures 3–5).

4. Discussion

Using the baseline data from a large population-based prospective study of incident PD we found significant associations between several CSF $A\beta$ species and lateral ventricular enlargement in PDCN and in the pooled sample of PD subjects. No significant correlation was detected between ventricular radial distance and CSF p-tau. T-tau showed significant associations with ventricular size only in the pooled sample. There were no significant associations between any CSF analyte and hippocampal radial distance.

$A\beta_{42}$, $A\beta_{40}$ and $A\beta_{38}$ are the three most common $A\beta$ peptides generated in the processing of amyloid precursor protein (APP)³⁹. $A\beta_{42}$ is particularly prone to aggregate and sequester in the form amyloid plaques in the human brain⁴⁰. Low CSF $A\beta$ is reported in both AD and PD¹⁰. The significance of the other two abundant $A\beta$ species - $A\beta_{40}$ and $A\beta_{38}$, on cognitive impairment in PD remains poorly understood. A recent study reported that CSF $A\beta_{42}/A\beta_{38}$ ratio as the measure that best discriminates between dementia with Lewy bodies and AD⁴¹. Ventricular expansion predicts future cognitive decline⁴² and often coincides with low levels of CSF $A\beta_{42}$ in cognitively normal persons^{13, 43}. All three $A\beta$ species were associated with memory impairment in our research cohort¹⁰. Taken together these data suggest a role of these CSF biomarkers for cognitive decline in PD.

We found a significant negative association between CSF t-tau with the left occipital and frontal horns in the pooled sample. CSF tau - a marker of axonal neuronal degeneration⁴⁴, has been reported to be normal¹⁰ or decreased in PDCN¹¹. Yet increased CSF tau levels were evident once cognitive impairment was clinically manifest⁹. As we follow the ParkWest cohort we will be able to investigate the development of late-occurring CSF tau changes and their relation to structural brain changes.

To our knowledge, this is the first study to investigate associations between hippocampal and lateral ventricle structural differences and neurodegenerative CSF biomarkers in PD. Our results support an association between CSF $A\beta$ measures and structural brain changes in newly diagnosed drug-naïve PD patients. The observed associations in the cognitively normal PD group agree with other reports^{10, 45} and suggests that both the CSF- and structural brain changes develop prior to manifestation of cognitive decline. In the PDMCI

group we found a trend level significant negative association with right occipital horn enlargement and A β 40. Yet the PDMCI subjects were on average older than the PDCN subjects and although we adjusted for age one can not fully exclude some residual effect. Thus one must consider the possibility that the observed ventricular changes are also related to aging. Future studies and our longitudinal analyses of the ParkWest data will be well positioned to address this issue.

In this study we did not find a significant correlation between WMH volumes and CSF A β markers in PD. This is in contrast to e.g. findings of a reported inverse relationship between the volume of chronic white matter change and CSF A β markers in a study of subjects with subjective cognitive impairment and MCI²⁰.

We failed to find an association between brain white matter change and cognition in this baseline ParkWest cohort, who had generally little WMH load¹⁹. Others have found a possible association between white matter change and PDD^{17, 18}, and an independent relation between WMH and cognitive impairment in PD¹⁷. White matter change has also been associated with cognitive impairment in patients with stroke⁴⁶. A recent study showed that increased WMH was associated with worsened motor performance⁴⁷, and may contribute to cognitive deficits in PD¹⁶. It remains to be seen if WMH will have more impact on cognition in the longitudinal follow up of our cohort, as has been suggested¹⁶.

A strong association between presence of ApoE4 and AD exists⁴⁸, and ApoE4 was higher in subjects with severe WMH after a lacunar infarct⁴⁹. We did not find significant differences between groups with or without cognitive impairment regarding presence of the ApoE4 allele in the Parkwest study¹⁵ or in a 10-year longitudinal study⁵⁰. This could be partly related to the low WMH burden found in our cohort and the fact that they had no infarcts. Another possible explanation is that ApoE4 does not act via vascular pathology in the PD population. In this study we found a lower percentage of ApoE4carriers in the cognitively impaired subjects (22%) than in the cognitively normal group (38%)(Table 1).

Thus it is possible that factors other than ApoE4 might drive neurodegeneration, leading to atrophy in early PD.

Our study has both strengths and limitations. A major strength is its longitudinal population-based prospective cohort design, and its focus on newly diagnosed PD. Our research subjects are well characterized. The use of state-of-the-art imaging analysis techniques to identify regionally specific disease associated changes, which are difficult to detect with more conventional analyses, is another strength of this study.

One limitation of our analyses is the small sample size of the PDMCI group with available CSF (N=18), which restricts our power to detect statistical significant correlations in this group. Without post-mortem brain examination the absence or concomitant AD pathology in our subjects cannot be ascertained. However, many consider low CSF A β 42, a widely accepted amyloid marker in AD, suggestive of concomitant AD pathology. *Post mortem* pathologic examinations of the ParkWest cohort are planned.

Our data show that CSF amyloid pathology correlates with ventricular expansion in PD, even in the earliest disease stages. The significance of the structural and CSF findings in respect to PD progression and cognitive decline will be ascertained as we proceed with the longitudinal analyses of the rich ParkWest dataset. The time course and sequence of the development of clinical, biochemical, structural and neuropathologic abnormalities in PD warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AD	Alzheimer's disease
Aβ₃₈	Amyloid beta 1-38
Aβ₄₀	Amyloid beta 1-40
Aβ₄₂	Amyloid beta 1-42
APOE	Apolipoprotein E
CSF	cerebrospinal fluid
MCI	mild cognitive impairment
MMSE	mini mental state examination
MRI	magnetic resonance imaging
PD	Parkinson's disease
PDD	Parkinson's disease and dementia
PDMCI	Parkinson's disease and mild cognitive impairment
PDCN	Cognitively normal PD subjects
p-tau	phosphorylated Tau
t-tau	total Tau
WMH	White matter hyperintensities
DLB	Dementia with Lewy bodies
UPDRS	Unified Parkinson's Disease Rating Scale

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Figure 1. 3D significance (left panel) and correlation maps (right panel) showing the associations of ventricular radial distance with age, center, APOE4 and WMH in the pooled sample. Areas in red and white in the statistical maps show statistical significance ($p < 0.01$).

Figure 2. 3D significance (left panel) and correlation maps (right panel) of the associations between CSF A β and tau species and ventricular radial distance in the pooled sample. Areas in red and white in the statistical maps show statistical significance ($p < 0.01$). All results are corrected for center, age and APOE.

Table 1

Comparison of demographic, clinical and CSF variables in PD controls and PDMCI (top) as well as ApoE4 carriers and noncarriers (bottom). Significant *p*-values (in bold) show group differences.

Variable	PDMCI (N=18)	PDCN (N=73)	P-value
Sex (m/f)	10/8	50/23	0.41
Age, years	71.7 (6.4)	65.1(9.9)	0.008
Education mean, years	11.4 (3.4)	11.4(3.5)	0.94
APOE4 allele present, N (%)	4 (22%)	28 (38.4%)	0.25
PD side, R/L/both	14/10/7	61/53/13	0.17
UPDRS – motor score	20.8 (9.0)	20.7(10.3)	0.72
H&Y on state score	1.9 (0.4)	1.8(0.6)	0.36
MMSE	26.7 (3.0)	28.3 (1.8)	0.035
CSF A β 38 pg/ml	417.2 (262.9)	467.5(277.3)	0.43
CSF A β 40 pg/ml	5545.9 (1422.6)	5820.2(2214.0)	0.84
CSF A β 42 pg/ml	363.0 (169.4)	363.3(208.2)	0.7
CSF t- tau pg/ml	227.3 (84.6)	221.2(127.5)	0.26
CSF p- tau pg/ml	53.1(24.6)	58.3(37.4)	0.86
Left hippocampus, mm ³	4603 (909)	4897 (866)	0.21
Right hippocampus, mm ³	4654 (992)	4868 (791)	0.33
Left frontal horn, mm ³	15461 (1217)	14939 (1316)	0.13
Left temporal horn, mm ³	265 (63)	237 (45)	0.18
Left occipital horn, mm ³	6251 (954)	5371 (1348)	0.011
Left whole ventricle, mm ³	21976 (1588)	20546 (2341)	0.016
Right frontal horn, mm ³	17553 (2666)	15821 (2989)	0.027
Right temporal horn, mm ³	404 (66)	392 (62)	0.48
Right occipital horn, mm ³	3696 (1169)	4089 (1050)	0.17
Right whole ventricle, mm ³	21653 (2967)	20302 (2919)	0.083
	APOE4 carriers (N=32)	APOE4 noncarriers (N=59)	P-value
CSF A β 38 pg/ml	483.5(255.5)	433.3(267.8)	0.240
CSF A β 40 pg/ml	6082.1(2018.4)	5550.3(2036.9)	0.391
CSF A β 42 pg/ml	350.1(195.7)	358.4(181.8)	0.842
CSF t- tau pg/ml	231.5(111.4)	211.8(118.1)	0.386
CSF p- tau pg/ml	61.4(33.6)	54.6(36.4)	0.275

Values denote means (SD). P values computed using two-sample t-test for continuous variables and a χ^2 test for sex. For tests with categorical variables or non-normal distribution a Kruskal Wallis test with a Mann Whitney test was used.

CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's disease Rating Scale. H&Y = Hoehn and Yahr score. Significant *p*-values are in bold.