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White matter hyperintensities, cerebrospinal amyloid-β and dementia in Parkinson's disease☆

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ABSTRACT

White-matter hyperintensities (WMHs) have been related to small-vessel disease, but also to amyloid-β (Aβ) vascular deposition, particularly in parieto-occipital regions. Low cerebrospinal fluid (CSF) $A\beta_{[1-42]}$ levels (biomarker of parenchymal and/or vascular Aβ deposition) and WMHs have been associated with Parkinson's disease (PD) and related dementia (PDD), separately but not in combination. We studied 50 subjects: 38 PD patients (19 non-demented [PDND] + 19 PDD) and 12 healthy-controls. Baseline regional WMHs from FLAIR MRI-sequences were dichotomized into none-to-mild vs. moderate-to-severe by an expert radiologist blind to clinical and CSF data using an adaption of the Age-Related White Matter Changes scale. Baseline CSF α-synuclein, τ and $A\beta_{[1-42]}$ levels were determined with ELISA techniques. Progression to dementia in PDND patients was clinically evaluated at 18 months. For analyses purposes patients were considered altogether (PDND + PDD) and separately (PDND vs. PDD). At baseline, moderate-to-severe parieto-occipital WMHs were significantly more frequent in PDD than in PDND ($p = 0.049$) and controls ($p = 0.029$), without significant differences in other regions. In regression models CSF Aβ was significantly associated in the entire PD cohort with moderate-to-severe parieto-occipital WMHs independently of age, vascular risk factors, APOE-4 and dementia. There were no associations with CSF α-synuclein and τ. Progression to dementia at 18 months was more frequent in patients with moderate-to-severe parieto-occipital WMHs and low CSF Aβ vs. those with none-to-mild parieto-occipital WMHs and normal CSF Aβ ($p = 0.007$). It remains to be seen whether the relationship between CSF Aβ and WMHs in PD and their association with PD-dementia is a reflection of not only parenchymal, but also vascular Aβ deposition.

1. Introduction

White matter hyperintensities (WMHs) seen in T2-derived sequences in brain MRI are frequent in the aging brain, being most often attributed to small-vessel disease [1]. WMHs have also been associated with vascular deposition of amyloid-β (Aβ), which besides aggregating in brain parenchyma is known to affect blood vessels as well (the so-called cerebral amyloid angiopathy; CAA) [1,2], especially in posterior (parieto-occipital) areas of the encephalon [3]. Accordingly, cerebrospinal fluid (CSF) levels of Aβ have been shown to be reduced in CAA [4].

Clinico-pathological studies have shown an association of white matter vascular damage and Aβ aggregates with cognitive impairment both in the general population and in Parkinson's disease (PD) [5–8], providing the rationale for assessing these pathologies in PD in vivo by means of biomarkers. Thus, WMHs have been associated with cognitive impairment and reductions in CSF Aβ levels have been observed in demented PD patients [9–13]. Furthermore, low CSF Aβ levels in PD have been associated cross-sectionally with specific neuropsychological deficits (verbal fluencies, visual object perception, memory impairment) [12,13], and longitudinally with cognitive worsening over time and increased dementia-risk [14–16]. Similarly, and in spite of lesser involvement relative to Alzheimer's disease or dementia with Lewy bodies in earlier studies [17,18], recent amyloid imaging reports have further supported the association between Aβ load and cognitive impairment in PD [19–22]. The apparent discrepancy between the relatively modest extent of WMHs or Aβ load in PD, on the one hand, and their significant association with cognitive impairment in PD, on the other, has been

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interpreted as a result of synergistic enhancement of different pathologies in a condition as heterogeneous as PD [5,7,22].

However, as to date the existing evidence on the relevance of WMHs and CSF Aβ in PD is limited to studies having looked at one or the other separately, not in combination. In the light of this, along with the fact that precisely posterior cortical cognitive deficits have been identified as dementia-predictors in PD [23], and that some studies have reported parieto-occipital WMHs in cognitively impaired PD patients [24,25], we hypothesized that WMHs (particularly the posterior ones) might be related to low CSF Aβ levels (rather than to other CSF biomarkers as α-synucelin or τ) and progression to dementia in PD. To this end, we conducted this proof-of-concept study with the aim of assessing the cross-sectional relationship between regional burden of WMHs and CSF Aβ levels in PD, as well as their longitudinal association with progression to dementia.

2. Methods

2.1. Design

Convenience case–control cohort study with cross-sectional and prospective longitudinal data.

2.2. Participants

Thirty-eight PD patients (19 non-demented [PDND], 19 demented [PDD]) and 12 control subjects without known neurological disorders who had taken part in CSF biomarkers studies were studied. These participants have been previously reported as part of a larger cohort [12,26]. No inclusion of part of the participants from the original cohort in the present study was exclusively owed to the lack of MRI due to usual contraindications (i.e., pacemaker), but there were no significant differences between excluded vs. included subjects (Mann–Whitney's *U*-test for age, years of education, UPDRS-III and MMSE scores in controls without vs. with MRI and in PD patients without vs. with MRI: $p > 0.05$; Fisher's exact test for sex in controls without vs. with MRI and in PD patients without vs. with MRI: $p > 0.05$). All participants provided their written informed consent after full explanation of all procedures. The study was approved by the Ethics Committee of our institution.

2.3. Baseline clinical definitions and assessments

The diagnosis and clinical assessments were performed by Movement Disorders specialists. All PD patients fulfilled the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank diagnostic criteria for clinically definite PD [27]. At the time of assessment, a structured interview was applied to classify PD patients as demented or not, relying on the Movement Disorder Society diagnostic criteria for PD-dementia [28], which requires the functional impairment criterion of the DSM-IV-R classification of dementia [29]. Severity of disease was assessed using Hoehn and Yahr staging [30]. The mini mental state examination (MMSE) [31] was applied as one of the first level global cognitive indicators recommended by the International Parkinson's Disease and Movement Disorders Society [32]. Vascular risk factors at baseline were recorded and dichotomized as present vs. absent. The Charlson's index (which considers heart, kidney, liver, lung, neurological, and infectious diseases as well as cancer) served as a co-morbidity indicator [33].

2.4. Baseline MRI acquisition and WMHs rating

AXIAL 2D FLAIR (slice thickening 3 mm, repetition-time 9280, echo time 90, inversion time 2500, 2 NEX GAP 0.9) was acquired with a TIM-TRIO-3 T scanner (Siemens, Germany), without sedation within three months of the lumbar puncture. FLAIR hyperintensities from all MRIs were scored by a single expert neuro-radiologist blind to clinical and CSF data (NB) using a previously published adaption of the European Task Force on Age-Related White Matter Changes (ARWMC) [34,35]. Briefly, FLAIR hyperintensities in different subcortical white matter regions (WMHs from frontal, temporal and parieto-occipital areas) and subcortical nuclei and brainstem (basal ganglia and infratentorial hyperintense lesions) were scored from 0 to 3 as follows considering both hemispheres altogether: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. For analyses purposes, the 0 to 3 scores were dichotomized as none-to-mild (≤1) vs. moderate-to-severe (>1).

2.5. APOE-4 determination

APOE was available for 9 (75%) of the controls and 35 (92%) of PD participants. APOE was genotyped through PCR amplification and HhaI digestion [36]. Cycling conditions were 94 °C for 5 min, 30 cycles of 94 °C for 30 s, annealing 50 °C for 30 s, extension at 72 °C for 30 s, and a final extension at 72 °C for 10 min. After a 3 h digestion with HhaI the fragments were separated in polyacrylamide gels and visualized through ethidium bromide staining. All the assays were analyzed using the StepOneTM real-time PCR system (Applied Biosystems, Foster City, CA).

2.6. Baseline CSF collection, processing, storage and analysis

All participants underwent lumbar tap in L2-3 space with a 22G needle after over-night fasting and under "off" medication. CSF was collected in polypropylene tubes, discarding the first 2 mL and centrifuging the next 10 mL at 4000G and 4 °C during 10 min, storing them in polypropylene aliquotes at −80 °C until analyses using commercial ELISA kits for total-α-synuclein (KHB0061, Invitrogen, Camarillo, CA, USA), and for total-τ and $A\beta_{1-42}$ (Innogenetics, Ghent, Belgium), as detailed elsewhere [12,26]. CSF Aβ is presented as concentrations in pg/mL and dichotomized according to the <500 pg/mL cut-off [12].

2.7. Longitudinal clinical assessment

PDND participants entered a clinical longitudinal phase with dementia as outcome as reported previously [15]. Longitudinal assessment consisted of routine clinical follow-up every 6 months and a final visit at 18 months when the same structured interview for PD-dementia classification used at baseline was applied again to check for progression to dementia (dementia-converters vs. non-converters).

2.8. Statistical analyses

Data were analyzed with SPSS program version 20.0 (IBM, New York, NY, USA) and are presented as absolute frequencies and percentages (qualitative variables) or medians and the respective inter-quartile ranges (IQR) (quantitative variables). Accordingly, data were compared with Fisher's exact test or Kruskal–Wallis/Mann–Whitney's *U* tests, respectively. The cross-sectional statistical analyses carried out were as follows: firstly, the proportions of participants with moderate-to-severe white matter changes were compared between controls, PDND and PDD patients; then, within group analyses (i.e., controls and PD patients both altogether and dichotomized as PDND and PDD) were performed to compare CSF Aβ levels between cases with none-to-mild vs. moderate-to-severe; finally, binary logistic regression models, resulting in odds ratios (OR) and their respective 95% confidence intervals (95%CI) were applied to assess the relationship between CSF Aβ as prognostic factor of WMHs in the entire PD cohort. Several models were run with adjust for the following potential modifiers: age (after its relationship with cognitive impairment, Aβ and WMHs), vascular risk factors (the most well recognized correlate of WMHs), presence of dementia at baseline (in order to rule out that the association between CSF Aβ and WMHs in the entire PD cohort might be driven by dementia rather