Cross-sectional and longitudinal associations of motor fluctuations and non-motor predominance with cerebrospinal τ and Aβ as well as dementia-risk in Parkinson’s disease

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Essential Information
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http://dx.doi.org/10.1016/j.jns.2016.12.064
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Article info
Article history:
Received 28 September 2016
Received in revised form 19 December 2016
Accepted 28 December 2016
Available online 30 December 2016
Keywords:
Parkinson’s disease-dementia
CSF Aβ
CSF τ
Endophenotypes
Non-motor symptoms
Motor fluctuations

Abstract
Experimental, neuropathological and cerebrospinal fluid (CSF) studies support τ and amyloid-β (Aβ) relevance in Parkinson’s disease (PD) related dementia. Lesser motor fluctuations (MFs) and non-motor features have also been related to PD-dementia. Yet, little is known about the association of MFs and non-motor symptoms with CSF τ and Aβ in PD. We hypothesized that lesser MFs and non-motor predominance are related to these CSF markers and dementia-risk in PD. We studied 58 PD patients (dementia at baseline, n = 21; dementia at 18-months, n = 35) in whom CSF Aβ and τ had been determined with ELISA techniques. MFs and a number of non-motor symptoms (apathy, anxiety, irritability, depression, visual hallucinations, spatial disorientation, memory complaints) over disease course were dichotomized as absent-mild vs. moderate-severe by retrospective clinical chart review blind to CSF findings. Non-motor predominance was defined as ≥3 non-motor symptoms (after the cohort-median of non-motor symptoms per patient) with ≥2 being moderate-severe and ≥1 having been present from onset, with all these being more disabling overall than motor features. Cross-sectionally, CSF biomarkers were non-parametrically compared according to dichotomized MFs and non-motor predominance. Longitudinally, dementia was the outcome (dependent variable), CSF markers, MFs and non-motor predominance were the predictors (independent variables), and potential modifiers as age, sex, and memory complaints were the covariates in binary regression models. Absent-mild MFs were associated with higher CSF τ markers and shorter time-to-dementia, while non-motor predominance and decreasing CSF Aβ independently increased longitudinal dementia-risk. In summary, absent-mild MFs, non-motor predominance and CSF τ and Aβ might define endophenotypes related to the timing or risk of dementia in PD.

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1. Introduction

Dementia is a frequent and devastating symptom of Parkinson’s disease (PD) [1]. Besides the spread of Lewy-type pathology to neocortical regions [2], the coexistence of Alzheimer’s disease (AD)-pathology has been implied in PD dementia (PDD) [3]. In this regard, τ and Aβ lesions have been associated with PDD, and a synergism between Lewy- and AD-type pathologies has been supported by clinico-pathological [3] and experimental studies [4,5]. In view of this and of the correlation of cerebrospinal fluid (CSF) levels of Aβ, τ and phospho-τ with senile plaques and neurofibrillary pathology, respectively [6], these CSF proteins have been tested as biomarkers of cognitive impairment in PD. Thus, high CSF τ and phospho-τ levels have been associated with impaired memory and naming [7], and low CSF Aβ levels with phonetic fluency and memory deficits [7,8]. Furthermore, longitudinal studies have found low CSF Aβ to predict cognitive worsening in PD [9–11]. There is also preliminary evidence that CSF τ and Aβ biomarkers are related independently of dementia to non-cognitive PD features as non-tremor predominance and the postural instability with gait disorder (PIGD) phenotype [12,13]. Interestingly, these motor phenotypes had been previously identified as risk factors for PDD [1,14]. Preceding studies have also hinted an association of cognitive impairment with lack of motor fluctuations (MFs) [15] and presence of non-motor symptoms [16] in PD. Still, none of those studies [1,12–16] addressed the relationship of MFs and non-motor symptoms with CSF τ and Aβ, nor how they
relate to dementia-risk in PD. Accordingly, we assessed the previously unexplored hypothesis that PD patients with lesser MFs and/or with non-motor predominance have higher CSF \(\tau\) and lower CSF A\(_{\beta}\) cross-sectionally, and that these clinical-CSF profiles are longitudinally related to dementia-risk.

2. Methods

2.1. Design

This is a hypothesis-driven cross-sectional and longitudinal single-centre convenience cohort study. Cross-sectional variables included baseline demographic, clinical and CSF features. The longitudinal endpoint was dementia at 18-month follow-up after CSF collection. Motor and non-motor features covered previous disease course up to baseline and were collected retrospectively by clinical charts review blind to the CSF variables. Progression to dementia was prospectively assessed as part of longitudinal projects on dementia-risk biomarkers in PD conducted at our unit [10,17]. The study main cross-sectional outcomes were the associations between MFs and non-motor symptoms with CSF \(\tau\) and A\(_{\beta}\) markers. The main longitudinal outcomes were the associations of these clinical and CSF variables with progression to dementia.

2.2. Participants

Fifty-eight patients from the Parkinson’s disease Movement Disorders Unit of our institution having taken part in previous CSF biomarkers protocols were included [7,10,17]. All fulfilled the United Kingdom Parkinson’s Disease Society (UKPDS) Brain Bank diagnostic criteria for definite PD [18], Hoehn & Yahr stages and the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) served as measures of motor severity [19,20]. Dementia was diagnosed using a structured interview based on the DSM-IV dementia criteria [21] and the Movement Disorder Society diagnostic criteria for PDD [22]. Levodopa equivalent daily dose (LED) was calculated too [23]. The study was approved by our Ethics Committee. All participants provided their informed consent.

2.3. Rating of MFs and of non-motor symptoms

A structured checklist covering the presence and severity of MFs and a series of non-motor symptoms over disease course was applied by two specialists in movement disorders (RM and MJM) blind to CSF findings and the longitudinal outcome by review of the clinical charts of the included patients. A number of non-motor symptoms (apathy, anxiety, irritability, depression, visual hallucinations, spatial disorientation and memory complaints) were selected on the basis of previous evidence linking them to dementia [22]. Non-motor symptoms having occurred in close temporal relationship to the introduction or change of medication were excluded.

With the information gathered from charts review, both specialists classified MFs and non-motor symptoms semiquantitatively by consensus. Thus, the classification of MFs was based on the functional impact on the daily living activities according to Part IV of the original UPDRS scale [20] as well as on the necessity to adjust the treatment over the course of the disease. As a result, and similarly to the approach previously used by others [24], the following semiquantitative classification of MFs was applied: 0 (absent); 1 (mild and short off-periods, not interfering with daily activities and well controlled with treatment adjustments); 2 (off-periods interfering with working and/or leisure daily activities, but not with basic daily living activities as walking, feeding or self-care, with just partial improvement after repeated treatment changes); 3 (severe off-periods resulting in inability to walk or take care of oneself during the off periods and not controllable with repeated treatment adjustments).

A similar approach was used to score non-motor symptoms: 0 (absent), 1 (mild and intermittent), 2 (moderate and intermittent, or mild but persistent), 3 (moderate and persistent, or severe regardless of the duration). A non-motor predominant phenotype was defined on the basis of the severity and frequency of non-motor symptoms, considering the cohort-median of non-motor symptoms per participant (see Section 3.1.3). Thus, non-motor predominance was considered in the presence of: a) at least three non-motor symptoms as consistent complaints across medical appointments; b) at least two moderate-to-severe non-motor symptoms; c) at least one non-motor symptom present at first clinical assessment; d) evidence from clinical records (i.e., patient’s complaints and need of treatment adjusts) that these non-motor symptoms were more troublesome than motor symptoms.

2.4. CSF collection, storage and analyses

All patients underwent lumbar puncture (LP) in L3–L4 space, using a 22G needle, between 8 and 10 AM, after overnight fasting and under off-medication. The first 2 mL of CSF were used for routine studies. The following 10 mL of CSF were collected in polypropylene tubes and immediately centrifuged for 10 min at 4000g and 4 °C, and stored at −80 °C in 300 µL polypropylene aliquots until analyses. After LP, patients stayed in bed for at least 2 h and were advised to increase water intake. All CSF samples were analyzed in duplicate using commercially available kits for ELISA studies of \(\tau\), \(\tau\) phosphorylated at threonine 181 (phospho-\(\tau\)), and A\(_{\beta}\) (Innotest \(\gamma\)-Antigen kit; Innotest PHOSPHO-\(\tau\) 181P; Innotest \(\beta\)-AMYLOID(1–42); Innogenetics, Ghent, Belgium).

2.5. Statistical analyses

All data were analyzed using SPSS 20.0 (IBM, New York, USA). No formal statistical power calculations were carried out. Yet, considering previous CSF studies with similar sample sizes [7,9,12], the available cohort was deemed likely to allow for detecting relevant associations. For analyses purposes, the semiquantitative classifications of MFs and non-motor symptoms were dichotomized into absent-to-mild vs. moderate-to-severe. Qualitative variables were treated as relative and absolute frequencies and compared with Fisher’s exact test. Quantitative variables were treated as medians and interquartile ranges, and compared by means of Mann-Whitney’s U test. Subsequently, binary logistic regression models applied in the field previously [3,10], allowed for further testing of significant findings from univariate analyses with adjust for potential modifiers. Binary logistic regression results are presented as odds ratios (OR) and the respective 95% confidence intervals (95% CI), with OR >1 indicating an increase in the outcome risk per each unit increase in the tested variable, with the opposite applying for OR <1 [25].

Thus, cross-sectionally, non-parametrical comparisons were conducted between patients with absent-to-mild vs. moderate-to-severe MFs and those with motor vs. non-motor predominance, with additional confirmatory binary logistic regressions with adjust for age and dementia at baseline. Longitudinally, conversion to dementia at 18-month follow-up among patients without dementia at baseline was the dependent variable (or outcome) in binary logistic regression models, where MFs, non-motor predominance, and CSF markers were the independent variables (or predictors), whereas age, sex, memory complaints, UPDRS-III and LEDD were co-variates (as potential modifiers). Lastly, the dementia outcome according to the combination of MFs and non-motor predominance is also provided as additional descriptive-only data (due to small subgroups size).

All analyses were two-tailed, with p-threshold at ≤0.05, without multiplicity adjusts due to the hypothesis-driven design [26].
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