Evolution of cerebrospinal fluid total α-synuclein in Parkinson's disease

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A B S T R A C T

Introduction: Cerebrospinal fluid (CSF) total α-synuclein is considered a potential biomarker for Parkinson’s disease (PD), but little is known about the evolution of this marker during the course of the disease. Our objective was to investigate whether CSF total α-synuclein concentrations change over time and are associated with motor and cognitive function in PD.

Methods: CSF total α-synuclein concentrations were quantified in 56 longitudinally followed PD patients, 27 of whom provided CSF repeatedly 2 and/or 4 years later. Another 18 subjects were included as controls. The samples were analyzed using two independent, validated ELISA methods: our recently developed and validated in-house ELISA and a commercial kit from BioLegend.

Results: CSF total α-synuclein levels did not distinguish PD patients from controls, displayed no substantial changes during a period of up to 4 years, and did not predict subsequent motor or cognitive decline. These findings were consistent for both analytical methods.

Conclusion: Our findings do not support the clinical utility of total α-synuclein as a single diagnostic or prognostic biomarker in PD.

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1. Introduction

Parkinson’s disease (PD) is characterized by a remarkable clinical heterogeneity, with substantial variation in disease progression and considerable overlap with other neurodegenerative diseases. Therefore, reliable biomarkers for diagnosis and prognosis of PD are urgently needed. Given the central role of α-synuclein aggregation in PD pathogenesis, and because α-synuclein levels are a major determinant of its neurotoxicity [1], it is of great interest to investigate the potential of α-synuclein as a diagnostic and prognostic biomarker. In this respect, cerebrospinal fluid (CSF) is considered the most promising source. Most, but not all previous studies report a trend towards lower total CSF α-synuclein levels in PD compared to controls, though with substantial overlap between diagnostic groups [2]. Only a few studies have reported longitudinal measurements of α-synuclein, also with conflicting results [3–6]. Hence, there is a need for additional longitudinal studies to track CSF α-synuclein changes during the disease course. We also examined whether total α-synuclein concentrations were associated with motor symptoms and neuropsychological performance.
and their changes over a period of up to 4 years. In addition, we compared total α-synuclein levels of PD patients with those of the controls.

2. Materials and methods

2.1. Patients

All PD patients were enrolled in the Norwegian ParkWest study, an ongoing, prospective, population-based, longitudinal cohort study of PD in Southwestern Norway [7]. Participants included a subset of 56 PD patients (median disease duration 4.8 years), of whom 27 also provided CSF at one or two follow-up visits 2 and 4 years later (Fig. 1 and Table 1). The patients were followed prospectively by movement disorders neurologists and fulfilled the National Institute of Neurological Disorders and Stroke [8] and UK Brain Bank [9] diagnostic criteria of PD from study entry to latest visit. Exclusion criteria were secondary parkinsonism and dementia during the first year of motor onset to eliminate patients with dementia with Lewy bodies and other dementias, including Alzheimer’s disease. All patients underwent a uniform and standardized examination program at each visit. Disease severity was determined using the Unified Parkinson’s Disease Rating Scale (UPDRS) [10] part II and III, and disease stage was evaluated using the Hoehn and Yahr scale (H&Y) [11]. Cognitive assessments included the Mini-Mental State Examination (MMSE) [12] as a measure of global cognition, and a neuropsychological test battery assessing the following domains: verbal memory (California Verbal Learning Test II [CVLT-II] [13], which included total immediate recall [sum of trials 1–5], short-delay, and long-delay free recall scores), attention (Stroop word reading and color naming) [14], executive functioning (Semantic Verbal Fluency Test [15], and Stroop interference condition) and visuospatial skills (Visual Object and Space Perception battery [VOSP] Silhouettes and Cube subtests) [16]. Severity of depressive symptoms was determined using the Montgomery and Asberg Depression Rating Scale (MADRS) [17].

2.2. Controls

The control group consisted of 18 subjects without known brain disease, who underwent elective neurological examination or orthopedic surgery at Stavanger University Hospital.

2.3. CSF sample treatment

CSF collection and sample treatment was conducted according to standardized procedures, as described elsewhere [18]. The CSF samples were centrifuged at 2000g for 10 min and frozen in polypropylene tubes at –80°C. The samples were subjected to one freeze-thaw event for aliquot purposes.

2.4. α-synuclein measurement

The in-house assay procedures and characteristics have been described in detail previously [19]. In brief, the ELISA assay fulfills the newest validation criteria [20], has a lower limit of quantification of 36.3 pg/ml and requires less than 15 μl CSF. The samples were analyzed in duplicates at the Neuroscience Research Laboratory at Stavanger University Hospital, Norway, with plate-to-plate variation below 6%. An identical set of CSF aliquots were sent to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Sweden for analysis with the commercial ELISA kit from BioLegend (#844101; BioLegend, San Diego, USA), with plate-to-plate variation below 5%. There was a high correlation between the two assays (r = 0.785, P < 0.001), which were independent in terms of site, date of analysis and personnel.

2.5. Hemoglobin measurement

To assess possible blood contamination as source of α-synuclein, the samples were analyzed for hemoglobin content using a commercial kit (#E88-135, Bethyl Laboratories, Montgomery, USA). Samples with hemoglobin concentrations above 200ng/ml were excluded from the study.

2.6. Statistical analysis

Standard curve fitting (4-parameter logistic fit), plotting of calibrator curves and calculation of total α-synuclein concentrations were performed using the Meso Scale Discovery Workbench 4.0 software (Meso Scale Discovery, Gaithersburg, USA). Descriptive statistics for continuous variables are presented as means for symmetrically distributed data, as geometric means for right skewed, small samples, or otherwise as medians, and with full ranges. Categorical variables are presented with counts and percentages. Between-group comparisons were performed by Mann-Whitney U for continuous variables. Within-patient comparisons were performed by paired samples t-tests for symmetrically distributed differences, or Wilcoxon paired signed rank tests for non-normally distributed data. Possible relationships between CSF total α-synuclein and clinical and neuropsychological performance at CSF sampling were assessed by linear regression analysis with adjustment for age and sex. To assess associations between CSF total α-synuclein and clinical and neuropsychological measures within 4 years after CSF sampling, we used linear random intercept models with adjustment for age, sex, and disease duration, and with time and CSF total α-synuclein included as main effects and with an interaction term, that measures the possible differential effect of levels of α-synuclein on progression slopes. Spearman’s rank correlation was used to assess strength of association between the two analytical methods. All analyses were conducted using SPSS 23 (IBM, Armonk, USA). Two-tailed P-values <0.05 were considered statistically significant. For multiple comparisons, Bonferroni correction was applied with two-tailed P-values <0.0036 (14 tests) considered significant.

2.7. Research ethics

All procedures were approved by The Norwegian Regional Committee for Medical and Health Research Ethics, and signed written informed consent was obtained from all participants.

Fig. 1. Overview of patients and time points of CSF sampling. 27 of the 56 patients provided CSF repeatedly 2 and/or 4 years later.
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