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Cerebrospinal fluid protein markers in PD patients after DBS-STN surgery—A retrospective analysis of patients that underwent surgery between 1993 and 2001

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ABSTRACT

Objective: Cerebrospinal fluid (CSF) markers of neurodegeneration [neurofilament light chain (NFL), total Tau (T-Tau)], tau pathology [phosphorylated tau (p-Tau)], glial cell damage or activation [glial fibrillary acidic protein (GFAP)], and brain amyloidosis [β-amyloid 1-42 (Aβ42)] are useful for diagnosis and prognosis in several neurodegenerative disorders. In this paper we investigate these markers and their relationship to key clinical milestones in patients with advanced Parkinson´s disease (PD) operated at our center with subthalamic nucleus deep brain stimulation (STN-DBS) for at least 15 years ago.

Patients and methods: Retrospective analysis of available cerebrospinal fluid and clinical data in PD-patients, 15 years or more after they underwent STN-DBS surgery. All PD-patients implanted with STN-DBS at Sahlgrenska University Hospital before January 1, 2001, were regularly assessed until January 10, 2018, or until death, or until lost to follow-up.

Results: Twenty three PD patients were operated with STN-DBS. Sixteen of these (six females and ten males) underwent at least one lumbar puncture (LP) immediately prior to or after STN-DBS. Their age at the latest available LP was 64 (55–75) years [median (range)], PD duration 20 (11–33) years, and Hoehn & Yahr (H&Y) stage 3 (2–4). Time between DBS operation and the last LP was 4.5 (0.3–10.8) years. Time from the last LP to the last follow up was 6 (0.1–18) years, and for the entire cohort 115 person-years. On January 10, 2018, four PD-patients (25%) were still alive.

All preoperative CSF marker levels were normal. Between two days and six months after DBS, NFL and GFAP levels increased sharply but they normalized thereafter in most patients, and were normal up to almost 11 years after neurosurgery. Over time, all patients deteriorated slowly. At the last follow up, H&Y was 5 (3–5) and 12/16 were demented.

There was no significant correlation between postoperative (> 6 months) CSF NFL, GFAP, T-Tau, p-Tau, β-amyloid levels and the presence of dementia, psychosis, inability to walk or need for nursing home at the time for LP, nor for presence of dementia at the last follow up or for death as of January 10, 2018.

Conclusion: CSF protein biomarkers remain normal despite long PD duration, severe disability, and chronic STN-DBS. They cannot be used for PD staging or prognostication but may indicate brain damage caused by other pathological factors.

1. Introduction

There is an unmet need for reliable diagnostic and progression markers in Parkinson's disease (PD). The diagnostic potential of cerebrospinal fluid (CSF) protein biomarkers has been intensely investigated during the last years, particularly in early PD. Tau proteins and β-amyloid 1-42 (Aβ42) are especially interesting considering their clinical usefulness in cognitive disorders such as Alzheimer's disease

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[1]. CSF total Tau (T-Tau), phosphorylated tau (p-Tau), Aβ42, and α-synuclein have been reported as slightly lower in early PD compared with healthy controls [2]. While the tau proteins and α-synuclein did not change significantly over 12 months, Aβ42 increased slightly but significantly in both groups [3]. Aβ42 was decreased in dementia with Lewy bodies and CSF neurofilament light chain (NFL) was increased in atypical parkinsonism compared with PD [4]. However, CSF NFL levels were similar in early PD and in healthy controls and did not significantly change over two years [5].

A substantial number of advanced PD-patients are treated with deep brain stimulation (DBS) commonly targeting the subthalamic nucleus (STN) or globus pallidus interna (GPi). There are few data on CSF markers in this subpopulation. We reported previously on eight advanced PD patients treated with STN-DBS in which CSF-NFL levels were normal preoperatively, increased sharply immediately postoperatively but normalized after 12 months [6]. Data from those patients are included in this study. Considering the heavy disease burden in advanced PD, particularly in respect to cognitive impairment and dementia, and the ongoing discussion regarding the impact of DBS on cognition [7,8], it is of interest to further investigate CSF markers in this growing PD-subpopulation.

In this study we present CSF data from a group of advanced PD patients operated with STN-DBS for more than 15 years ago and followed at our center.

2. Patients and methods

Patients and methods have already been described in a previously published paper [9]. In summary, we conducted a retrospective analysis of all available CSF, demographical, clinical and STN-DBS status data from subjects with advanced PD implanted with STN-DBS systems before January 1, 2001, at our center. Data was retrieved from clinical files and was based on examinations and interviews, conducted by movement disorders specialist, psychiatrists, other physicians, psychologists, nurses, physiotherapists, occupational therapists and social workers. CSF data included date of lumbar puncture (LP), and levels of biomarkers for neurodegeneration (NFL, T-Tau), tau pathology (p-Tau), glial cell damage or activation [glial fibrillary acidic protein (GFAP)], and brain amyloidosis (Aβ42). The presence of key clinical milestones and their date of onset were recorded. The chosen key clinical milestones reflecting the overall function of the PD-patients in daily living were the occurrence of (1): dementia [defined as a score of 4 on Unified Parkinson`s Disease Rating Scale (UPDRS) 1.1 [10]] (2); psychosis [a score of 3 or 4 on UPDRS 1.2 (formed hallucinations with loss of insight and/or delusions)] (3); inability to walk [H&Y stage 5 (need for wheelchair)]; (4); loss of autonomy (need for nursing home or personal assistant 24 h a day, every day); and (5) mortality. Information about the date of death was obtained from the Swedish Mortality Registry.

All patients have been regularly followed up at our center after operation, until death or until they were lost to follow-up. Some are still followed-up. For the purpose of this study, data was collected as recorded at the follow up visits, except for information regarding survival which was updated January 10, 2018.

2.1. Cerebrospinal fluid analysis

LP were performed in the supine position. CSF was collected in polypropylene tubes. All analyzes were performed as part of clinical routine testing by board-certified laboratory technicians. The laboratory was accredited by the Swedish Board for Accreditation and Conformity Assessment.

For measurements of CSF-NFL concentrations, an in house ELISA with a polyclonal capture antibody was used [11,12].

CSF-T-tau concentration was determined using a sandwich ELISA (Innotest hTAU-Ag, Fujirebio, Ghent, Belgium) specifically constructed to measure all tau isoforms irrespectively of phosphorylation status, as previously described [13].

Tau phosphorylated at threonine 181 (P-tau181) was measured using a sandwich ELISA method (INNOTEST® PHOSPHO-TAU(181 P), Innogenetics, Ghent, Belgium), as described previously in detail [14]. Aβ 1-42 levels were determined using a sandwich ELISA (INNOTEST® ß-AMYLOID(1-42), Innogenetics, Gent, Belgium), specifically constructed to measure Aβ containing both the first and 42nd amino acid, as previously described [15]. In this assay, the monoclonal antibody 21F12, which is highly specific for the C-terminus of Aβ42 was used for capture, and 3D6, which is specific to the N-terminus was used as detector.

The ELISA CSF-GFAP was performed as previously described [16].

The upper limits of the reference range, the mean inter-assay coefficient of variation, and the limits for detection for CSF protein markers are presented in Supplementary files (Supplementary Table 1).

2.2. Ethics

In eight patients, all medical procedures including LP were performed for clinical purposes only. Eight patients participated in a previously published study aiming at studying brain damage markers after STN-DBS and gave their consent to participate [6]. That study and the retrospective design of this study including data retrieval from clinical files were approved by the Regional Ethical Board at the University of Gothenburg.

2.3. Statistics

Descriptive statistics were used to describe the population, when appropriate. Values are expressed as median and range (minimum-maximum), unless otherwise specified. The Related samples Wilcoxon Signed Rank Test was used to analyze differences before and after DBS. Correlations between categorical variables were investigated through cross-tabulation with Fisher's exact test. Associations were calculated with linear-, logistic- or Cox-regression, as appropriate. Because levels of CSF protein markers are related to age, all regressions were adjusted for age at LP. When a patient underwent several LP-s, only data from the last one were used in the association analysis. In order to minimize the impact of the acute neurosurgical brain tissue damage on the long term interpretation of clinical and CSF data, only data obtained at more than six months postoperatively were used in these calculations. All tests were two tailed with $p \leq 0.05$ as the level of significance. SPSS statistics package version 22 was used for analysis.

3. Results

3.1. Demographics and PD related clinical scores (Supplementary Tables 2 and 3)

The patients of this study are part of a larger cohort presented in a previous publication [9]. CSF data was available from 16 PD patients (10 male and 6 female) who were implanted with STN-DBS systems between December 1993 and January 1, 2001. Their age at PD onset was 42 (34–55) years [median (range)]. At the time for surgery their age was 63 (50–71) years, their PD duration 20 (10–24) years, and their Hoehn & Yahr stage 3 (2.5–4) [17] and none was demented. Their age at the latest available LP age was 64 (55–75) years, PD duration was 20 (11–33) years, and Hoehn & Yahr stage 3 (2–4). The median time from DBS-electrode implantation to the last LP was 4.5 (0.3–10.8) years. Following surgery, motor function improved in all patients. At the last follow-up, all PD-patients were significantly worse compared with baseline (preoperatively), with a Hoehn & Yahr stage of 5 (3–5) ($p < 0.05$, Related samples Wilcoxon Signed Rank Test) and 12/16 patients were demented.