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Great Minds.
The value of cerebrospinal fluid $\alpha$-synuclein and the tau/$\alpha$-synuclein ratio for diagnosis of neurodegenerative disorders with Lewy pathology

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Background and purpose: Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD) are three of the most common neurodegenerative disorders. Up to 20% of these patients have the wrong diagnosis, due to overlapping symptoms and shared pathologies. A cerebrospinal fluid (CSF) biomarker panel for AD is making its way into the clinic, but an equivalent panel for PD and DLB is still lacking. Using well-defined, community-based cohorts and validated analytical methods, the diagnostic value of CSF total-$\alpha$-synuclein (t-$\alpha$-syn) alone and in combination with total tau (t-tau) in newly diagnosed patients with PD, DLB and AD was determined.

Methods: Cerebrospinal fluid concentrations of t-$\alpha$-syn were assessed using our validated in-house enzyme-linked immunosorbent assay in 78 PD patients, 20 AD patients, 19 DLB patients and 32 controls. t-tau was measured using a commercial assay. Diagnostic performance was assessed by receiver operating characteristic curve analysis.

Results: Compared to controls (mean 517 pg/ml), significantly lower levels of CSF t-$\alpha$-syn in patients with PD (434 pg/ml, 16% reduction, $P = 0.036$), DLB (398 pg/ml, 23% reduction, $P = 0.009$) and AD (383 pg/ml, 26% reduction, $P = 0.014$) were found. t-$\alpha$-syn levels did not differ significantly between PD, DLB and AD. The t-tau/t-$\alpha$-syn ratio showed an improved performance compared to the single markers.

Conclusion: This is the first study to compare patients with PD, DLB and AD at the time of diagnosis. It was found that t-$\alpha$-syn can contribute as a teammate with tau in a CSF biomarker panel for PD and DLB, and strengthen the existing biomarker panel for AD.

Introduction

Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD) are three of the most common neurodegenerative diseases worldwide. Despite some fundamental differences in underlying causes and pathologies, there is also a substantial overlap of symptoms and pathological features [1,2]. Therefore, major challenges for the management of PD, DLB and AD are diagnostic and prognostic inaccuracy, which highlight the need for biomarkers to aid in clinical decision making.
One of the pathological features that has been observed most frequently in PD, DLB and AD is α-synuclein (α-syn) aggregation into Lewy bodies (LBs) [3]. LBs are best known for their role in PD and DLB, hence termed synucleinopathies, but are also found in up to 60% of all patients with AD upon autopsy [4].

Cerebrospinal fluid (CSF) α-syn has been proposed as a biomarker for neurodegenerative diseases with LB pathology. For PD, the majority of previous studies report reduced CSF total-α-syn (t-α-syn) levels in PD patients compared to controls [5,6]. However, the findings are inconsistent as several studies showed no differences [6]. It has also been suggested that t-α-syn may improve the diagnostic and prognostic performance of the AD biomarker panel [7]. The interest for α-syn in AD pathology further increased with the notion that α-syn interacts with amyloid-β (Aβ) and tau to promote mutual aggregation and thereby increase neurodegeneration and worsen the prognosis [8]. Two meta-analyses focusing on AD [9] and DLB [10] conclude that CSF t-α-syn is significantly higher in AD compared to the other neurological disorders assessed, including PD and DLB, but does not differ significantly between AD and controls [9], DLB and controls or DLB and PD [10]. However, the findings are inconsistent as several studies report that t-α-syn did not differentiate between DLB and AD [6].

The Investigating Synuclein Consortium [11] and others have identified the need for further research, specifically using well-defined patient groups with uniform diagnostic criteria, validated assays and proper pre-analytical sample handling. In the light of this, CSF t-α-syn was measured using a validated in-house enzyme-linked immunosorbent assay (ELISA) in patients with PD, AD and DLB from two renowned longitudinal cohort studies specifically designed for the analysis of biomarkers.

Materials and methods

Study participants

The PD group consisted of 78 newly diagnosed, drug-naïve patients from the Norwegian ParkWest study [12], a prospective, population-based, longitudinal cohort study investigating the incidence, neurobiology and prognosis of PD. All met diagnostic criteria of PD [13] at their final study visit. Exclusion criteria were atypical and secondary parkinsonism as well as dementia development during the first year of motor onset to ensure exclusion of patients with DLB and AD.

Cerebrospinal fluid from 20 AD and 19 DLB patients were obtained from the Norwegian DemWest study, a prospective, longitudinal cohort study of patients with suspected or newly diagnosed dementia [14]. A diagnosis of AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria [15], and a diagnosis of DLB was made according to the Diagnostic and Statistical Manual of Mental Disorders IV [16]. All patients met criteria of AD or DLB, respectively, at their final study visit.

All patients underwent comprehensive, standardized clinical assessments by experienced movement disorder and dementia experts [14,17]. Motor severity was determined using the Unified Parkinson’s Disease Rating Scale (UPDRS) part III [18], and global cognition was determined by the Mini-Mental State Examination (MMSE) [19]. For PD, disease stage was evaluated using the Hoehn and Yahr scale [20].

The control group was a set of 32 subjects without any known brain disease, who underwent elective neurological examination or orthopaedic surgery at Stavanger University Hospital. Only MMSE and demographic data were obtained for the control group.

Pre-analytical sample handling

Lumbar puncture and CSF collection was conducted according to standardized procedures after overnight fasting, as described previously [17]. Briefly, the freshly drawn CSF samples were centrifuged at 2000 g for 10 min at 4°C, and frozen in polypropylene tubes at −80°C. Prior to analysis, the samples were subjected to one freeze–thaw event for aliquotation purposes. The samples were thawed on ice and kept on ice until analysis.

Total-α-syn and t-tau measurement

The CSF samples were analysed using our recently developed and validated in-house t-α-syn ELISA, as described before [21]. This assay recognizes the 140 amino acid monomeric form of α-syn and showed high correlation with the BioLegend assay for t-α-syn [21]. Plate-to-plate variation was below 9%. t-tau was measured using a commercial kit (V-Plex; Meso Scale Discovery, Rockville, MD, USA) according to the manufacturer’s instructions. For three PD samples, the t-tau concentration was below the detection limit of the assay and they were therefore removed from the analysis. The plate-to-plate variation was below 11.1%. All analyses were performed at the
Neuroscience Research Laboratory at Stavanger University Hospital, Norway.

Haemoglobin measurement

To assess possible blood contamination as a source of \( \alpha \)-syn, the samples were analysed for haemoglobin content using a commercial kit (Bethyl Laboratories, Montgomery, AL, USA). Samples with haemoglobin levels over 200 ng/ml were excluded from the study.

Statistical analysis

A four-parameter logistic fit of standard curves as well as calculation of t-\( \alpha \)-syn and t-tau concentrations were done with the Mesoscale Discovery Workbench 4.0 software (Meso Scale Discovery). Descriptive statistics for continuous variables are presented as mean with standard deviations. Categorical variables are presented as counts and percentages. Between-group comparisons were performed with Kruskal–Wallis tests for continuous variables or Pearson chi-squared tests for categorical variables. The strengths of correlations between continuous variables are presented as Spearman’s rank correlation coefficients. Between group comparisons for CSF data were determined by ANCOVA followed by simple planned contrast analysis entering log-transformed CSF values and adjusting for age and sex. Primary comparisons were normal controls (NCs) versus PD, DLB or AD. Secondary comparisons were between PD, DLB and AD. Receiver operating characteristic (ROC) curve analyses were used to calculate the area under the curve (AUC) and \( P \) values. AUC values were classified as follows: 0.9–1.0 excellent, 0.8–0.9 good, 0.7–0.8 fair, 0.6–0.7 poor, and below 0.6 fail. Cut-off values were determined using the Youden index. ROC curves were plotted in Excel (Microsoft, Redmond, WA, USA). All analyses were conducted using SPSS 24 (IBM, Armonk, NY, USA). Two-tailed \( P \) values <0.05 were considered statistically significant.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics. All participants provided written informed consent. This study complies with the Declaration of Helsinki.

Results

In this study, a total of 149 subjects were included to determine the ability of CSF t-\( \alpha \)-syn alone and in combination with t-tau to discriminate between patients with newly diagnosed PD (\( n = 78 \)), DLB (\( n = 19 \)) and AD (\( n = 20 \)), as well as NCs (\( n = 32 \)) (group characteristics in Table 1). The mean t-\( \alpha \)-syn concentrations were significantly lower in PD, DLB and AD patients than in the control group (\( P = 0.036 \), \( P = 0.009 \) and \( P = 0.014 \), respectively). Amongst the disease groups, the mean t-\( \alpha \)-syn concentrations were highest in PD, intermediate in DLB and lowest in AD (Fig. 1a). However, the observed differences between the three disease groups were not significant (all \( P > 0.253 \)). t-tau was increased in the AD group compared to controls (\( P = 0.050 \)) and compared to PD (\( P = 0.041 \), Fig. 1b). The DLB group showed a similar pattern to AD, but the differences were not statistically significant.

There was a positive correlation between t-\( \alpha \)-syn and t-tau across all diagnostic groups (\( \rho = 0.696–0.788 \), all \( P < 0.001 \), Table S1). Correlations of clinical parameters (MMSE, UPDRS part III, disease duration and age) with t-\( \alpha \)-syn and t-tau are presented in

### Table 1 Demographic data and CSF concentrations

|                | NCs   | PD    | DLB   | AD    | \( P \) value |
|----------------|-------|-------|-------|-------|--------------|
| Number of cases| 32    | 78    | 19    | 20    |              |
| Age (years)    | 67.9 (8.5) | 66.5 (8.3) | 73.3 (6.7) | 73.3 (10.9) | 0.001        |
| Number of women (%) | 17 (53.1%) | 22 (28.2%) | 6 (31.6%) | 14 (70.0%) | 0.002        |
| Education (years) | 10.7 (3.4) | 11.5 (3.3) | 10.0 (3.0) | 10.0 (3.0) | 0.147        |
| Disease duration (years)\(^a\) | –     | 2.3 (1.9) | 2.2 (1.9) | 1.4 (1.0) | 0.050        |
| MMSE           | 28.8 (1.0) | 27.7 (2.4) | 23.3 (4.3) | 23.4 (3.5) | <0.001       |
| UPDRS part III | –     | 21.3 (9.9) | 14.3 (11.4) | 2.0 (2.5) | <0.001       |
| t-\( \alpha \)-syn (pg/ml) | 517 (215) | 434 (223) | 398 (148) | 383 (147) | 0.027        |
| t-tau (pg/ml)  | 403 (236) | 392 (310)\(^b\) | 469 (356) | 678 (448) | 0.212        |
| t-tau/t-\( \alpha \)-syn | 0.77 (0.3) | 0.87 (0.4)\(^b\) | 1.13 (0.7) | 1.71 (0.8) | <0.001       |

\( \alpha \)-syn, total-\( \alpha \)-synuclein; t-tau, total tau; UPDRS, Unified Parkinson’s Disease Rating Scale. Data are presented as mean (SD). \( P \) values for age, education, disease duration, MMSE and UPDRS were determined by Kruskal–Wallis \( H \) test. \( P \) value for sex was determined by ANCOVA, entering log-transformed CSF concentrations and adjusting for age and sex.\(^a\)Time from the patient recalling the first symptoms to the clinical diagnosis; \(^b\)\( N = 75 \).

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Table S2. Notably, MMSE was negatively correlated with t-α-syn within NCs, PD and AD (only significant within NCs, \( q = 0.452, P = 0.010 \)), but was positively correlated within DLB (\( q = 0.606, P = 0.006 \)).

When exploring the t-tau/t-α-syn ratio, ANCOVA with age and sex entered as covariates demonstrated significant differences between the groups (\( P < 0.001 \)). Simple planned contrast analyses revealed significant differences between AD and NCs (\( P < 0.001 \)) and between AD and PD (\( P < 0.001 \), Fig. 1c, Table S3).

Across the disease groups, the t-tau/t-α-syn ratio was lowest in PD. The diagnostic performance of t-α-syn, t-tau and the ratio was determined by ROC curve analysis (Table 2). Whilst the single CSF markers had a fair or poor diagnostic performance, the t-tau/t-α-syn ratio resulted in an improved diagnostic performance for all group comparisons except PD versus NCs (55% sensitivity and 95% specificity). For PD versus AD the AUC increased from 0.58 for t-α-syn (70% sensitivity and 54% specificity) and 0.73 for t-tau (70% sensitivity and 76% specificity) to 0.83 for the t-tau/t-α-syn ratio (70% sensitivity and 88% specificity).

**Discussion**

The most important findings of this study, assessing CSF levels of t-α-syn alone and combined with t-tau in newly diagnosed patients with PD, DLB, AD and NCs, are (i) that t-α-syn levels were significantly lower in PD, DLB and AD than in NCs and (ii) that the use of the t-tau/t-α-syn ratio instead of the single markers significantly improved the diagnostic performance for most group comparisons.

Previous findings on CSF α-syn in PD, DLB and AD have been inconsistent, which could be explained by differences in pre-analytical sample handling,
quantification methods, inclusion criteria and level of diagnostic evidence. This study makes a significant contribution to the field through analysis of well-characterized cohorts of patients with long clinical follow-up period and strict inclusion and exclusion criteria, standardized sample treatment, and our validated and highly sensitive t-α-syn ELISA. Our findings match the studies showing reduced t-α-syn concentrations in PD versus NCs [6], and it was found that t-α-syn was also significantly lower in AD and DLB compared to NCs.

The decrease of CSF t-α-syn in PD and DLB may be attributed to aggregation and deposition of t-α-syn into LBs, their primary pathological hallmark. For AD, our findings of reduced t-α-syn compared to NCs are in line with reports by Öhrfelt et al. [22] and Parnetti et al. [23] who proposed a lower secretion into CSF due to synaptic loss in AD. Many studies, however, have reported t-α-syn levels in AD being about equal to or slightly higher compared to NCs [9]. This discrepancy might be caused by differences between the respective AD cohorts. The AD patients in our study were newly diagnosed and thus our findings might be reflective of an early disease state. Interestingly, in our study, t-α-syn tended to be higher in AD patients with lower MMSE (correlation not significant) and thus supposedly with higher synaptic loss [24]. For DLB a positive correlation between t-α-syn and MMSE was observed which could indicate that synaptic loss has contributed to the reduced t-α-syn levels in the DLB group.

For t-α-syn, no significant differences between PD, DLB and AD were found. Recent evidence suggests that t-α-syn in combination with other markers can provide discriminatory information between diseases [7,23,25–29]. Tau and α-syn interact and promote each other’s aggregation, and co-occurrence of tau and t-α-syn inclusions are frequent in PD, DLB and AD [1]. A positive correlation was found between t-α-syn and t-tau which is in line with previous studies [7,25,28,30–32]. Two previous studies have reported an improved diagnostic performance using the t-tau/t-α-syn ratio in distinguishing PD from controls [23,26]. In our study with newly diagnosed, drug-naive patients, it was found that the t-tau/t-α-syn ratio did not improve the diagnostic performance of NCs versus PD or DLB versus PD. However, it is shown for the first time that the t-tau/t-α-syn ratio significantly improved diagnostic performance for NCs versus AD, PD versus AD and DLB versus AD. Thus, the t-tau/t-α-syn ratio can strengthen the AD core biomarker panel.

The strengths of this study are the strict inclusion criteria for each diagnostic group and that patients were diagnosed and followed by experienced movement or dementia experts over a long time to ensure highest diagnostic accuracy. All patients were newly diagnosed and drug-naive and thus at an early disease stage, which is when the differential diagnosis is the most difficult. A limitation of this study is the relatively small group sizes of the AD and DLB patients.

A panel of CSF markers consisting of t-tau, phosphorylated tau and Aβ1–42 has been shown to correlate with AD pathology with high sensitivity and specificity, and has had a large impact on the field. A counterpart that correlates well with α-syn pathology, however, is still to be discovered. Our results validate findings that the t-tau/t-α-syn ratio increases the diagnostic value of tau and t-α-syn, and should be included in the development of a biomarker panel for PD, DLB and AD. The identification of a diagnostic biomarker panel to improve the early and more accurate diagnosis of these disorders will be tremendously

### Table 2 Results of receiver operating characteristic curve analysis

|          | t-α-syn | t-tau | t-tau/t-α-syn |
|----------|---------|-------|---------------|
| **NCs versus PD** |         |       |               |
| AUC      | 0.625   | 0.550 | 0.560         |
| P value  | 0.040   | 0.414 | 0.324         |
| Sensitivity% | 82.1    | 48.0  | 54.7          |
| Specificity% | 43.8    | 68.8  | 62.5          |
| Cut-off value or ratio | 556.6   | 295.4 | 0.74          |
| **NCs versus DLB** |         |       |               |
| AUC      | 0.674   | 0.522 | 0.707         |
| P value  | 0.039   | 0.793 | 0.014         |
| Sensitivity% | 78.9    | 26.3  | 73.7          |
| Specificity% | 56.3    | 87.5  | 68.8          |
| Cut-off value or ratio | 469.2   | 606.9 | 0.77          |
| **NCs versus AD** |         |       |               |
| AUC      | 0.691   | 0.705 | 0.867         |
| P value  | 0.022   | 0.013 | <0.001        |
| Sensitivity% | 80.0    | 70.0  | 85.0          |
| Specificity% | 56.3    | 68.8  | 75.0          |
| Cut-off value or ratio | 474.6   | 461.2 | 0.92          |
| **PD versus DLB** |         |       |               |
| AUC      | 0.545   | 0.572 | 0.644         |
| P value  | 0.543   | 0.335 | 0.054         |
| Sensitivity% | 68.4    | 52.6  | 78.9          |
| Specificity% | 53.8    | 53.3  | 50.7          |
| Cut-off value or ratio | 404.3   | 327.3 | 0.76          |
| **PD versus AD** |         |       |               |
| AUC      | 0.580   | 0.731 | 0.830         |
| P value  | 0.271   | 0.002 | <0.001        |
| Sensitivity% | 70.0    | 70.0  | 70.0          |
| Specificity% | 53.8    | 76.0  | 88.0          |
| Cut-off value or ratio | 402.3   | 465.9 | 1.29          |
| **DLB versus AD** |         |       |               |
| AUC      | 0.542   | 0.663 | 0.739         |
| P value  | 0.653   | 0.082 | 0.011         |
| Sensitivity% | 40.0    | 70.0  | 55.0          |
| Specificity% | 78.9    | 68.4  | 94.7          |
| Cut-off value or ratio | 302.1   | 451.7 | 0.74          |

AD, Alzheimer’s disease; AUC, area under the curve; DLB, dementia with Lewy bodies; NCs, normal controls; PD, Parkinson’s disease; t-α-syn, total-α-synuclein; t-tau, total tau.
important for early diagnosis, patient management and clinical trials.

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Disclosure of conflicts of interest

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Figure 2 ROC analyses. Diagnostic performance of t-α-syn, t-tau and the t-tau/t-α-syn ratio in distinguishing NCs from PD, DLB or AD (a)–(c), and PD from DLB, PD from AD, and DLB from AD (d)–(f). Overview of the diagnostic performance of the t-tau/t-α-syn ratio (g)–(h).
Ole-Bjørn Tysnes: has been invited speaker for GSK, Orion Pharma, Pfizer, UCB and Lundbeck. He has participated in an advisory board for Lundbeck. Dag Aarsland: has received research support and hono-
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Data accessibility statement
Anonymized data can be obtained by request from a qualified investigator for the purposes of replicating procedures and results. More information regarding the data from the Norwegian ParkWest study and contact information can be found at http://www.park west.no/.

Supporting Information
Additional Supporting Information may be found in the online version of this article:

Table S1. CSF biomarker correlations (Spearman’s rho).
Table S2. Correlations (Spearman’s rho).
Table S3. P values for simple planned contrasts from
ANCOVA with age and sex as covariates.

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