Accuracy of a Panel of 5 Cerebrospinal Fluid Biomarkers in the Differential Diagnosis of Patients With Dementia and/or Parkinsonian Disorders

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Objective: To assess the ability of 5 cerebrospinal fluid (CSF) biomarkers to differentiate between common dementia and parkinsonian disorders.

Design: A cross-sectional, clinic-based study.

Participants: Cerebrospinal fluid samples (N = 453) were obtained from healthy individuals serving as controls and from patients with Parkinson disease (PD), PD with dementia (PDD), dementia with Lewy bodies (DLB), Alzheimer disease (AD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD).

Setting: Neurology and memory disorder clinics.

Main Outcome Measures: Cerebrospinal fluid biomarker levels in relation to clinical diagnosis.

Results: Cerebrospinal fluid levels of α-synuclein were decreased in patients with PD, PDD, DLB, and MSA but increased in patients with AD. Cerebrospinal fluid levels of β-amyloid 1-42 were decreased in DLB and even further decreased in AD. Cerebrospinal fluid levels of total tau and hyperphosphorylated tau were increased in AD. Multivariate analysis revealed that these biomarkers could differentiate AD from DLB and PDD with an area under the curve of 0.90, with α-synuclein and total tau contributing most to the model. Cerebrospinal fluid levels of neurofilament light chain were substantially increased in atypical parkinsonian disorders (ie, PSP, MSA, and CBD), and multivariate analysis revealed that the level of neurofilament light chain alone could differentiate PD from atypical parkinsonian disorders, with an area under the curve of 0.93.

Conclusions: Ascertainment of the α-synuclein level in CSF somewhat improves the differential diagnosis of AD vs DLB and PDD when combined with established AD biomarkers. The level of neurofilament light chain alone may differentiate PD from atypical parkinsonian disorders.


Primary neurodegenerative disorders cause substantial suffering of affected individuals, family members, and caretakers and large costs for society. The prevalence of many neurodegenerative disorders, the most common being Alzheimer disease (AD) and Parkinson disease (PD), will increase significantly worldwide in the coming decades as a consequence of aging populations. Because of overlapping symptoms, especially during early disease stages, it is often difficult to clinically distinguish PD from atypical parkinsonian disorders, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). The neuropathologies of parkinsonian disorders form 2 broad clusters depending on the type of pathologic protein inclusion. Synucleinopathies are characterized by intracellular aggregates consisting mainly of α-synuclein, which are found in Lewy bodies and Lewy neurites in PD, PD with dementia (PDD), and dementia with Lewy bodies (DLB), as well as in glial cytoplasmic inclusions in MSA. In contrast, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are characterized by intraneuronal deposition of tau protein and are denoted tauopathies.

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There is also a significant overlap in symptoms and brain pathologies be-
between the dementia disorders, including AD, DLB, and PDD. Alzheimer disease, the most common form of dementia, is characterized by accumulation of intraneuronal deposition of the hyperphosphorylated tau protein (neurofibrillar tangles) and extracellular aggregates of β-amyloid (amyloid plaques). However, amyloid accumulation often also occurs in patients with DLB and in some patients with PDD.2

Several studies on potential disease-modifying treatments are under way; these are directed toward different pathology-specific mechanisms, such as amyloid accumulation, hyperphosphorylation of tau, and aggregation of α-synuclein.3 Thus, there is a need for methods that can determine which brain pathology (or pathologies) underlies the symptoms of individual patients, rather than classifying patients according to clinical syndromes, so that the affected individuals can be treated appropriately. Moreover, methods for early diagnosis are required, since future disease-modifying therapies will likely be most efficient if initiated when the patients exhibit only subtle symptoms, ie, before severe and irreversible neurodegeneration has occurred.4 Methods for early and accurate diagnosis would also be important in clinical practice, since early and accurate diagnosis speeds initiation of relevant symptomatic therapies, avoids medication errors and unnecessary investigations, and reduces insecurity for the patient. For example, many antipsychotic drugs sometimes used for patients with AD can be detrimental for patients with DLB.5

Methods available today can facilitate early diagnosis of AD. Several studies7-10 have shown that cerebrospinal fluid (CSF) levels of β-amyloid 1-42 (Aβ1-42) are reduced and the levels of total tau (T-tau) and phosphorylated tau (P-tau) are elevated in patients with AD compared with cognitively healthy individuals. However, these biomarkers cannot reliably distinguish AD from DLB (and in some cases, PDD) because of overlapping Aβ and tau pathology. Patients with AD typically do not exhibit α-synuclein pathology. Therefore, a panel of biomarkers reflecting these pathologies might better distinguish the disease entities.

In contrast to AD, there are no established CSF biomarkers for clinical use in PD. Although the results are conflicting, most studies11-13 have shown that patients with PD and MSA exhibit slightly but significantly lower levels of α-synuclein in CSF vs the levels in healthy controls. To our knowledge, the levels of α-synuclein in CBD are unknown. The CSF level of neurofilament light chain (NF-L) protein, reflecting subcortical axonal damage, is present at normal levels in patients with PD. However, results of some promising studies15-20 suggest that NF-L can differentiate patients with PD from patients with PSP, MSA, and CBD.

Overall, no single biochemical marker has been found that exhibits enough specificity and sensitivity to be used to differentiate the most common primary neurodegenerative disorders. There is a lack of large studies comparing all relevant differential diagnostic groups and simultaneously analyzing many of the most promising CSF biomarker candidates. We therefore evaluated the potential diagnostic accuracy of a panel of 5 biomarkers in the CSF of patients with parkinsonism and/or dementia. A newly developed assay (Luminex) was used for simultaneous quantification of α-synuclein, Aβ1-42, T-tau, and P-tau; NF-L was analyzed separately with conventional enzyme-linked immunosassay.

METHODS

STUDY PARTICIPANTS

The present study was performed at Skåne University Hospital and Sahlgrenska University Hospital. We analyzed 453 CSF samples from patients with PD (n=90), AD (n=48), PDD (n=33), DLB (n=70), PSP (n=45), MSA (n=48), and CBD (n=12) and from healthy individuals serving as controls (n=107). The patients diagnosed with PD met the National Institute of Neurological Disorders and Stroke diagnostic criteria for PD.21 Patients diagnosed with PDD met the clinical diagnostic criteria for dementia associated with PD according to Emre et al.22 Patients who received a diagnosis of MSA met the consensus statement on the diagnosis of that disorder.23 Patients who received the diagnosis PSP met the criteria according to the report of the National Institute of Neurological Disorders and Stroke–Society for Progressive Supranuclear Palsy International Workshop.24 Patients with CBD were diagnosed in accordance with guidelines.25 Patients who received an AD diagnosis met the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) criteria of dementia26 and the criteria of probable AD defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.27 Patients with DLB met the consensus criteria according to McKeith et al.28 The 107 controls underwent cognitive testing and neurologic examination by a physician, and individuals with objective cognitive or parkinsonian symptoms were not included as controls in the present study.

CSF SAMPLES AND HEMOGLOBIN TEST

Cerebrospinal fluid was collected in polypropylene tubes and gently mixed to avoid gradient effects. All samples were centrifuged within 30 minutes at +4°C (Skåne University Hospital) or at +21°C (Sahlgrenska University Hospital) at 2000g for 10 minutes to remove cells and debris. Samples were stored in aliquots at −80°C pending biochemical analysis. Hemoglobin levels in CSF samples were analyzed using a human hemoglobin enzyme-linked immunosassay kit (Bethyl Laboratories, Inc) according to the manufacturer’s protocol. Only samples with hemoglobin levels below 1000 ng/L (405 of the 453 CSF samples) were included when studying CSF α-synuclein with nonparametric statistical methods because our experiments using artificially blood-contaminated CSF showed that α-synuclein concentrations started to increase in CSF samples with hemoglobin concentrations above this cutoff point, probably resulting from leakage of α-synuclein from red blood cells (data not shown). These results are in agreement with previous findings.29

STANDARD PROTOCOL APPROVAL, REGISTRATION, AND PATIENT CONSENT

The ethics committees of Gothenburg University and Lund University approved this study. All the participants provided consent for research and the study was performed in accord with the provisions of the Helsinki Declaration.

METHODS FOR BEAD-BASED XMAP TECHNOLOGY

A newly developed multiplex assay (Luminex) was used for simultaneous quantification of α-synuclein, Aβ42, T-tau, and P-tau. The method is described in detail in the eMethods and eTable (http://www.archneurol.com).
The Pearson Wallis test was performed, followed by the Mann-Whitney test to compare demographic and CSF baseline data between groups, a nonparametric Kruskal-Wallis test was performed using the orthogonal projections to latent structures (OPLS) algorithm implemented in commercial software (SIMCA P+, version 12; Umetrics). In brief, the algorithm identifies the direction, termed a score vector, in the multidimensional orthogonal space spanned by the analytes that best separates the predefined groups. Receiver operating characteristic analysis was performed on the individual analytes in addition to the projections onto the score vector from the OPLS-DA using commercial software (GraphPad Prism, version 5; GraphPad Software).

ASSOCIATIONS BETWEEN DEMOGRAPHIC VARIABLES AND CSF BIOMARKERS

The demographic data and CSF biomarker levels of all 453 participants are reported in the Table. The NF-L level correlated with more severe parkinsonian symptoms (measured with the Hoehn-Yahr staging scale) in pa-
tients with PD (R_s = 0.33; P = .002) and PSP (R_s = 0.41; P = .008) and with worse cognitive performance (measured with the Mini-Mental State Examination) in patients with AD (R_s = −0.35; P = .02). However, the NF-L level did not correlate with the duration of disease in these conditions (P > .05), indicating that NF-L is associated with disease severity and not disease duration.

Increased age was associated with higher levels of NF-L in many of the diagnostic groups, ie, in controls (R_s = 0.60; P < .001), patients with PD (R_s = 0.47; P < .001), and those with DLB (R_s = 0.40; P = .001). Moreover, the α-synuclein level correlated with age in the controls (R_s = 0.20; P = .048), patients with PD (R_s = 0.26; P = .03), and those with MSA (R_s = 0.40; P = .01).

CSF BIOMARKER LEVELS IN DIFFERENT DIAGNOSTIC GROUPS

Univariate Statistical Analysis

In the patient groups with predominant dementia, individuals with a diagnosis of PDD had increased levels of P-tau (13%) and NF-L (41%) compared with patients with PD without dementia (P < .01) (Figure 1D and E and Table). Patients with DLB had decreased levels of Aβ1-42 (−27% to −29%) and increased levels of NF-L (41% to 60%) compared with both controls and patients with PD (P < .001) (Figure 1B and Table). However, patients with AD had even further decreased levels of Aβ1-42 (−19% to −37%) and increased levels of T-tau (78% to 130%) and P-tau (98% to 120%) upon comparison with controls and patients with PDD or DLB (P < .001) (Figure 1B, C, and D and Table). The CSF α-synuclein was reduced in patients with DLB and in PDD when compared with the control group as a whole, but this change was not statistically significant (Figure 1A and Table). Because patients with PDD or DLB were older than the controls (Table), these patient groups were also compared with age-matched controls, resulting in significantly lower levels of α-synuclein (−19% to 24%) in patients with PDD or DLB (P < .05). In contrast, patients with AD had higher levels of α-synuclein (39% to 62%) compared with controls and patients with PDD or DLB (P < .001) (Figure 2A and Table).

In the patient groups with predominant parkinsonism, we found that the levels of α-synuclein were decreased in patients with PD (−18% to 21%) and MSA (−16% to 20%) compared with controls and patients with PSP (P < .05) (Figure 1A and Table). The levels of NF-L were increased in all patients with atypical parkinson-
ism, ie, PSP (226%-271%), MSA (316%-374%), or CBD (332%-392%), compared with both controls and patients with PD (P < .001) (Figure 1E and Table). The levels of T-tau and P-tau were decreased (~22% and ~6%, respectively) in patients with PD compared with the levels in the controls (P < .05) (Figure 1C and D and Table). The T-tau levels were also decreased in patients with PSP (~12%) and MSA (~14%) compared with the controls (P < .05) (Figure 1D and Table).

To be able to adjust for potential confounding effects of age, sex, and hemoglobin levels in CSF, we performed analysis of covariance, analyzing log-transformed biomarker levels separately with age, sex, and CSF hemoglobin levels included in the models. We found that the α-synuclein level was decreased in patients with PD, PDD, DLB, and MSA when compared with controls and patients with PSP (P < .05). Patients with AD had increased levels of α-synuclein when compared with all other diagnostic groups (P < .05). The level of Aβ1-42 was decreased in patients with DLB or AD when compared with all other diagnostic groups (P < .05), but the Aβ1-42 levels were decreased even further in AD compared with DLB (P < .01). The levels of T-tau and P-tau were increased in AD when compared with all other diagnostic groups (P < .001) except for T-tau in patients with CBD. The levels of NF-L were increased in all patient groups when compared with the controls (P < .05), but patients with atypical parkinsonian disorders (PSP, MSA, and CBD) had higher levels compared with patients in all other diagnostic groups (P < .001). Adjusting for Hoehn-Yahr scale scores in the group with parkinsonism showed that there were still significant differences in NF-L levels between atypical parkinsonian disorders (PSP, MSA, and CBD) when compared with PD or PDD (P < .05). When adjusting for Mini-Mental State Examination scores in the dementia groups, we found that NF-L levels were increased in DLB and AD (but not in PDD) when compared with the controls (P < .05).

Multivariate Statistical Analysis

Multivariate discriminant analysis (OPLS-DA) was used to study the diagnostic accuracy when using all 5 biomarkers simultaneously (Figure 2). In the patient groups with predominant dementia, we found that the 5 biomarkers could differentiate AD from DLB and PDD, with an area under the curve (AUC) of 0.90 (95% CI, 0.85-0.96), a sensitivity of 90% (95% CI, 83%-95%), and a specificity of 81% (95% CI, 67%-91%) (Figure 2A). When separating AD from DLB alone, the multivariate discriminant analysis resulted in an AUC of 0.89 (95% CI, 0.82-0.95), a sensitivity of 88% (95% CI, 78%-95%), and a specificity of 81% (95% CI, 67%-91%). Total tau and α-synuclein contributed most to the diagnostic accuracy of these models (Figure 2B).

In the patient groups with predominant parkinsonism, the 5 CSF biomarkers could differentiate patients with PD from patients with atypical parkinsonian disorders (PSP, CBD, and MSA), with an AUC 0.93 (95% CI, 0.89-0.97), a sensitivity of 85% (95% CI, 76%-91%), and a specificity of 92% (95% CI, 85%-97%) (Figure 2C). In this model, NF-L contributed most to the diagnostic accuracy and NF-L alone resulted in diagnostic accuracy similar to that of the multivariate model (Figure 2D). Similar results were obtained when PD was separated from PSP and CBD (Figure 2C and D). Very similar results were obtained when using values not corrected for differences between clinical sites (eFigure).

The present study showed that a panel of 4 CSF biomarkers, ie, T-tau, α-synuclein, P-tau, and Aβ1-42, can be used to differentiate patients with AD from patients with DLB or PDD; NF-L alone can be used to separate patients with PD from those with atypical parkinsonism.

**Figure 2.** Diagnostic accuracy of cerebrospinal fluid (CSF) biomarkers in patients with dementia or parkinsonism. Multivariate discriminant analysis (DA) was performed using the orthogonal projections to latent structures (OPLS) algorithm. Receiver operating characteristic curves were calculated for both OPLS-DA and for each analyte, including α-synuclein (αSyn), β-amyloid 1-42 (Aβ1-42), total tau (T-tau), phosphorylated tau (P-tau), and neurofilament light chain (NF-L). The areas under the curve (AUC) are given. A, Patients with Alzheimer disease (AD) (n = 48) were compared with patients with dementia with Lewy bodies (DLB) and those with Parkinson disease with dementia (PDD) (n = 103). B, Corresponding variable importance in projection (VIP) plot illustrates the relative contributions of T-tau, αSyn, P-tau, Aβ1-42, and NF-L to the separation between patients with AD vs patients with DLB or PDD; C, Patients with Parkinson disease (PD) (n = 90) were compared with patients with atypical parkinsonism, ie, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA) (n = 105); D, Corresponding VIP plot illustrates the relative contributions of NF-L, P-tau, αSyn, T-tau, and Aβ1-42 to the separation between patients with PD vs patients with PSP, MSA, and CBD. Error bars represent the 95% CI.

**Comment**
(ie, PSP, MSA, and CBD). The CSF α-synuclein level was decreased in patients with synucleinopathies (PD, PDD, DLB, and MSA) when compared with controls and patients with PSP or AD.

Ascertaining the levels of Aβ1-42, T-tau, and P-tau in CSF can aid in the diagnostic workup of patients with suspected AD, and these markers exhibit a high diagnostic accuracy for differentiating patients with AD from healthy individuals. Separating AD from other dementias is more complicated because of overlapping pathologies (eg, AD-related pathology is often observed in patients with DLB). Several studies have evaluated the ability of CSF Aβ1-42, T-tau, and P-tau levels to differentiate between patients with AD, DLB, or PDD, but the results have been conflicting and overlaps between patient groups have been problematic. Anderson et al found that the levels of CSF tau were increased and Aβ42 were decreased in AD vs PDD and the levels in DLB were intermediate. The levels of α-synuclein have been reported to be lower in patients with DLB when compared with the levels in patients with AD, but this has not been confirmed. In the present study, we confirmed that CSF T-tau and P-tau levels are increased in patients with AD as compared with patients with PDD and DLB. Moreover, we showed that although Aβ1-42 is reduced in PDD and DLB, the levels are further reduced in AD, which is consistent with neuropathologic data showing that Aβ-related pathology is more pronounced in AD compared with DLB and PDD. Lewy body pathology is typically absent in AD, and the present study showed a clear difference in the levels of α-synuclein between patients with AD and patients with PDD or DLB. The observed increased levels of α-synuclein in patients with AD could be interpreted as a consequence of leakage of α-synuclein from degenerating neurons, which has been demonstrated by an increase in the levels of α-synuclein in other neurodegenerative disorders with widespread neurodegeneration, such as Creutzfeldt-Jakob disease. An alternative explanation might be that α-synuclein enters the CSF from a peripheral source by crossing the blood-brain barrier.

Most important, we found that the diagnostic accuracy of a panel of 5 biomarkers, representing tau-, Aβ- and α-synuclein–related pathology, was high enough to be of clear value in the clinical workup of differentiating patients with AD from those with PDD and DLB (AUC, 0.90). The diagnostic accuracy of these 5 CSF biomarkers, when differentiating AD from DLB, is at least in the same order of magnitude as that obtained with dopamine transporter imaging and with a lower cost.

Biomarkers in CSF or plasma for early diagnosis of PD are, in contrast to AD, not yet established. Several studies have reported reduced levels of CSF α-synuclein in patients with PD when compared with controls but without the sensitivity and specificity to give it clinical relevance. and results have been conflicting. We showed that CSF levels of α-synuclein decreased in synucleinopathies (ie, PD, PDD, DLB, and MSA) compared with the levels in controls, but these changes were modest. Therefore, CSF measurements of α-synuclein alone would be of little use for early diagnosis of PD when compared with conditions with normal levels of α-synuclein, such as healthy aging, arthritis, and essential tremor. Recently, one study measuring the CSF levels of oligomeric α-synuclein showed more clear-cut differences when separating patients with PD from healthy elderly individuals.

There is also a clinical need to discriminate between different parkinsonian disorders (ie, PD vs atypical parkinsonism). Consistent with a study by Mollenhauer et al, we found that patients with PD or MSA had lower levels of α-synuclein, but the overlap with PSP and CBD is too large to be clinically useful. Other studies have suggested that CSF T-tau may aid in differentiating PD from atypical parkinsonism, which was not confirmed by our study. A few promising studies have shown that the CSF levels of NF-L can be used to differentiate PD from MSA, PSP, and, in one study, CBD. For example, Holmberg et al showed that NF-L can differentiate patients with PD vs patients with MSA and PSP with a sensitivity of 78% and a specificity of 80%. Our study confirmed that the CSF levels of NF-L are increased in atypical parkinsonian disorders, and the observed diagnostic accuracy of NF-L (AUC, 0.93) is high enough to be clinically relevant. Increased CSF levels of NF-L in patients with parkinsonism warrant further investigations in the clinical setting, with more detailed examination and imaging, looking for signs consistent with PSP, MSA, or CBD.

In the present study, higher levels of NF-L, but none of the other CSF biomarkers, correlated with a more severe disease stage in patients with PD, PSP, and AD, which might reflect an increase in axonal pathology over time in these patients. Neurofilament light chain might be a disease severity biomarker that could be used in clinical trials when evaluating the effects of new disease-modifying therapies. If a certain therapy results in a lowering of NF-L levels in pilot studies, this might indicate that the treatment can reverse disease progression, increasing the chance that the clinical outcome will be favorable in future large and longitudinal clinical trials.

One of the strengths of the present study was that we simultaneously studied the diagnostic value of 5 CSF biomarkers (α-synuclein, Aβ1-42, T-tau, P-tau, and NF-L), which together reflect the major pathologies observed in primary neurodegenerative disorders resulting in dementia and/or parkinsonism. To our knowledge, only 1 previous study has investigated the diagnostic accuracy of CSF biomarkers when including a relevant number of patients from most of the important diagnostic groups affected by tau, Aβ, and/or α-synuclein pathology; however, that study did not investigate NF-L and patients with CBD were not included. Moreover, to our knowledge, the present study is the first to evaluate the added value of combining several CSF biomarkers simultaneously in the differential diagnosis of all these disorders. In the present study, only 3 patients had undergone neuropathologic validation of the clinical diagnosis (2 with DLB and 1 with PSP), which is a limitation of the study. For example, the control group might have included individuals with preclinical disease, and we might consequently have underestimated the specificity of some of the biomarkers. However, all patients had been examined in highly specialized clinics focused on clinical
Determining the level of α-synuclein in CSF improves the differential diagnosis of AD vs DLB and PDD when combined with established AD biomarkers, ie, T-tau, P-tau, and Aβ1-42. The diagnostic accuracy of these biomarkers was high enough to be of clear value in the clinical setting when differentiating AD from DLB and PDD (AUC, 0.90). Moreover, we found that NF-L can differentiate PD from atypical parkinsonian disorders (AUC, 0.93). Together with earlier published data, our results indicate that these 5 CSF biomarkers might have clinical value in the differential diagnosis of dementia and/or parkinsonism. Longitudinal studies are needed to evaluate the additional value of α-synuclein and NF-L as diagnostic biomarkers during the early stages of the disease processes of these disorders.

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Author Contributions: Drs Hall, Ohrfelt, and Hansson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed, commented on, and approved the final report. Drs Hall and Ohrfelt contributed equally to the present work.

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CONCLUSIONS

Conflict of Interest Disclosures: None reported.

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Online-Only Material: The eMethods, eTable, and eFigure are available at http://www.archneurol.com.

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