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Featured Article

Cerebrospinal fluid α-synuclein contributes to the differential diagnosis of Alzheimer's disease

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Abstract

Introduction: The ability of Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (amyloid β peptide 1–42, total tau, and phosphorylated tau) to discriminate AD from related disorders is limited. Biomarkers for other concomitant pathologies (e.g., CSF α-synuclein [α-syn] for Lewy body pathology) may be needed to further improve the differential diagnosis.

Methods: CSF total α-syn, phosphorylated α-syn Ser129, and AD CSF biomarkers were evaluated with Luminex immunoassays in 367 participants, followed by validation in 74 different neuropathologically confirmed cases.

Results: CSF total α-syn, when combined with amyloid β peptide 1–42 and either total tau or phosphorylated tau, improved the differential diagnosis of AD versus frontotemporal dementia, Lewy body disorders, or other neurological disorders. The diagnostic accuracy of the combined models attained clinical relevance (area under curve ~0.9) and was largely validated in neuropathologically confirmed cases.

Conclusions: Combining CSF biomarkers representing AD and Lewy body pathologies may have clinical value in the differential diagnosis of AD.

Keywords: Alzheimer's disease; Differential diagnosis; Biomarkers; Cerebrospinal fluid; α-synuclein

1. Introduction

Investigations using biochemical measures in cerebrospinal fluid (CSF) as Alzheimer's disease (AD) biomarkers have shown great promise, and such CSF biomarkers have been incorporated into recent guidelines for informed diagnosis of AD [1]. Specifically, CSF markers of core AD pathology (i.e., amyloid β peptide 1–42 [$A\beta_{42}$] reflecting Aβ in plaque burden, and total tau [t-tau] and phosphorylated tau [p-tau] for assessing neurofibrillary tangles in the brain) provide both high sensitivity and specificity (80% or above) in differentiating patients with AD or mild cognitive impairment (MCI; prodromal AD) from healthy controls (HCs) [2–4]. However, the diagnostic accuracy of these CSF biomarkers in the differential diagnosis of AD and other dementias is limited (40%–80% sensitivity and specificity)

Conflicts of interest: The authors declare that they have no conflicts of interest to report.

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due to a substantial overlap in the CSF levels of these proteins [4–9]. A recent large-scale international multicenter study [5] suggested that the limited utility of these core CSF biomarkers to discriminate AD from a variety of related disorders could be due to the overlap in the underlying primary pathologies, and introduction of additional CSF biomarkers reflecting other types of pathologies could be of value to optimize the differential diagnosis [4,5], though reliance on clinical diagnoses might underestimate the accuracy of CSF biomarkers [10].

Among the concomitant non-AD type pathologies in AD, α-synuclein (α-syn)-positive Lewy bodies (LBs), the pathological hallmark of another family of neurodegenerative diseases including Parkinson disease (PD) and dementia with Lewy bodies (DLB), can be observed in up to 50% of familial and sporadic AD patients at autopsy [11–13]. We have reported that CSF total α-syn and phosphorylated α-syn at Ser129 (pS129) help differentiate PD from AD and other related neurodegenerative diseases [14–16]. More recently, we also found that CSF total α-syn improved the diagnostic and prognostic performance of CSF $A\beta_{42}$ and tau in AD [17,18]. In this study, to test whether inclusion of CSF α-syn that represents brain LB pathology could improve the differential diagnosis of AD and other dementias, we further evaluated the utility of CSF total α-syn and pS129 in the differential diagnosis in a relatively large clinical cohort, followed by validating our findings in a separate cohort of neuropathologically confirmed cases.

2. Methods

2.1. Subjects

Two cohorts of research participants were recruited at the AD Core Center, the Penn Memory Center, the Frontotemporal Degeneration (FTD) Center, the Amyotrophic Lateral Sclerosis (ALS) Center, the PD and Movement Disorder Clinic, and the Penn Udall Center for Parkinson's Research at the UPenn [19]. The clinical or discovery cohort (n = 540) of clinically diagnosed participants included 165 AD, 105 MCI, 70 FTD (including 60 behavioral variant FTD and 10 corticobasal syndrome), 79 LB disorders (LBD; including 16 DLB and 63 PD or PD with dementia [PDD]), 41 ALS, 11 progressive supranuclear palsy (PSP), and 69 HC (see Table 1 and Supplementary Table 1). The validation cohort contained 102 neuropathologically confirmed cases, including 40 AD, 23 frontotemporal lobar degeneration with and without AD (FTLD; 17 FTLD, and 6 FTLD-AD), 30 PD or Lewy body–related pathology with and without AD (LRP) (three PD, four PD-AD, 21 LRP-AD, and two LRP-TDP), and six ALS (see below, Table 2, and Supplementary Table 2 for more details; note that three HC cases with an unremarkable burden of any significant brain pathology were not included in the analyses in the present study due to the small case number). The clinical diagnoses were made by applying clinical diagnostic criteria for AD [1], behavioral variant FTD [20], corticobasal syndrome [21], primary progressive aphasia [22], DLB [23], PD or PDD [24,25], ALS [26], PSP [27], and HC as previously reported [19,28,29]. For the purposes of this study, patients diagnosed as corticobasal syndrome, behavioral variant FTD, FTD-motor neuron disease, progressive nonfluent aphasia, and semantic dementia were classified as FTD, whereas subjects with AD and logopenic progressive aphasia were classified as AD. As per current conventions, the term FTD was used for the clinical diagnosis, and the term FTLD for the neuropathologically confirmed diagnoses. Informed consent to be included in research studies and to perform the autopsy was obtained in all cases from the patients or legal representatives in accordance with the Pennsylvania state law. The study and all protocols were approved by the Institutional Review Boards of the University of Pennsylvania and the University of Washington.

2.2. CSF collection and CSF measurements

All CSF samples were obtained by lumbar puncture as described previously, and samples were immediately stored at −80°C until analysis [30]. CSF total α-syn and pS129 levels were measured at the University of Washington by using Luminex immunoassays as previously described [14,16]. CSF data for $A\beta_{42}$, t-tau, and p-tau were obtained at the University of Pennsylvania by using the INNO-BIA AlzBio3™ Luminex assay reagents (Innogenetics, Ghent, Belgium) [30–32]. CSF hemoglobin levels were measured as an index of red blood cell contamination, using a human hemoglobin ELISA quantitation kit (Bethyl Laboratories Inc, Montgomery, TX, USA) as previously described [14].

2.3. Tissue collection and neuropathological assessment

Tissue collection procedures have been previously described [19]. Briefly, a neuropathological diagnosis of AD was assigned if the probability was intermediate or high [33]. The diagnoses of FTLD-TAU, FTLD-TDP, and DLB were based on established criteria [23,34]. FTLD-TAU cases included cases with a diagnosis of argyrophilic grain disease, PSP, tangle predominant senile dementia, and corticobasal degeneration. See Supplementary Methods for more details.

2.4. Statistical analysis

All analyses were performed in SPSS 18.0 (IBM, Chicago, IL, USA) or Prism 6.0 (GraphPad Software, La Jolla, CA, USA). Immunoassay data (CSF total α-syn, pS129, $A\beta_{42}$, t-tau, and p-tau) were Log10 transformed to generate a more normally distributed data set, and the transformed data were used in all analyses. Correlations between biomarkers are reported as Pearson correlation coefficients. One way analysis of variance followed by Tukey post hoc test was used to compare group means. Receiver operating characteristic (ROC) curves for analytes, controlling for