CSF VILIP-1 predicts rates of cognitive decline in early Alzheimer disease

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ABSTRACT

Objective: Measures of neuronal damage/dysfunction are likely good surrogates for disease progression in Alzheimer disease (AD). CSF markers of neuronal injury may offer utility in predicting disease progression and guiding prognostic and outcome assessments in therapeutic trials. Visinin-like protein-1 (VILIP-1) has demonstrated potential utility as a marker of neuronal injury. We here investigate the utility of VILIP-1 and VILIP-1/Aβ42 in predicting rates of cognitive decline in early AD.

Methods: Individuals with a clinical diagnosis of very mild or mild AD (n = 60) and baseline CSF measures of VILIP-1, tau, p-tau181, and Aβ42 were followed longitudinally for an average of 2.6 years. Annual assessments included the Clinical Dementia Rating (CDR), CDR-sum of boxes (CDR-SB), and global composite scores. Mixed linear models assessed the ability of CSF biomarker measures to predict rates of cognitive decline over time.

Results: Baseline CSF VILIP-1 and VILIP-1/Aβ42 levels predicted rates of future decline in CDR-SB and global composite scores over the follow-up period. Individuals with CSF VILIP-1 ≥560 pg/mL (corresponding to the upper tercile) progressed much more rapidly in CDR-SB (1.61 boxes/year; $p = 0.0077$) and global scores (−0.53 points/year; $p = 0.0002$) than individuals with lower values (0.85 boxes/year and −0.15 points/year, respectively) over the follow-up period. CSF tau, p-tau181, tau/Aβ42, and p-tau181/Aβ42 also predicted more rapid cognitive decline in CDR-SB and global scores over time.

Conclusion: These findings suggest that CSF VILIP-1 and VILIP-1/Aβ42 predict rates of global cognitive decline similarly to tau and tau/Aβ42, and may be useful CSF surrogates for neurodegeneration in early AD. ***Neurology*® 2012;78:709–719**

GLOSSARY

Aβ42 = amyloid-beta 1–42; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CDR-SB** = Clinical Dementia Rating–sum of boxes; **LP** = lumbar puncture; **NFT** = neurofibrillary tangle; **VILIP-1** = Visinin-like protein-1; **WAIS** = Wechsler Adult Intelligence Scale; **WMS** = Wechsler Memory Scale; **WU-ADRC** = Washington University Alzheimer's Disease Research Center.

The aggregation and deposition of amyloid-β and tau, the 2 key proteins involved in Alzheimer disease (AD) pathogenesis, are estimated to begin years prior to the onset of cognitive impairment.[1,2] However, it is only after a threshold of neuronal loss is reached in vulnerable brain regions that the first signs of cognitive impairment appear.[3]

Several lines of evidence suggest that neuronal and synaptic loss is the best surrogate for disease progression and cognitive decline in AD.[2,4] While CSF tau and amyloid-beta 1–42 (Aβ42) each predominantly reflect a specific AD pathology, neuronal injury/neurodegeneration likely represents the cumulative outcome of different pathologic substrates. Therefore, CSF markers of neuronal injury, along with CSF tau and Aβ42, may offer utility in predicting disease progression and future cognitive decline in the early stages of disease.

Supplemental data at www.neurology.org

Supplemental Data

From the Department of Neurology (R.T., J.-M.L., J.C.M., D.M.H.), Hope Center for Neurological Disorders (R.T., J.-M.L., D.M.H.), Charles F. and Joanne Knight Alzheimer's Disease Research Center (R.T., J.C.M., D.M.H.), Department of Pathology and Immunology (J.H.L.), and Department of Developmental Biology (D.M.H.), Washington University School of Medicine, St. Louis, MO.

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Visinin-like protein-1 (VILIP-1) is a neuronal calcium-sensor protein[5] which has demonstrated utility as a marker of neuronal injury.[6,7] We have previously demonstrated that CSF VILIP-1 and VILIP-1/Aβ42 offer diagnostic and prognostic utility for AD, and may provide useful biomarker surrogates for neurodegeneration.[8] We here investigate the utility of CSF VILIP-1 and VILIP-1/Aβ42 in predicting rates of cognitive decline in a well-characterized cohort of individuals with very mild and mild AD who were followed for 2–3 years.

METHODS

Participants and clinical assessments. We identified participants (n = 60) enrolled in longitudinal studies of healthy aging and dementia through the Washington University Alzheimer's Disease Research Center (WU-ADRC) who met the following criteria: 1) age 60 years or older, 2) clinical diagnosis of very mild (Clinical Dementia Rating [CDR] 0.5) or mild (CDR 1) AD, 3) baseline CSF measures of VILIP-1, tau, phosphorylated tau-181 (p-tau181), Aβ42, and Aβ40, 4) 2 or more annual cognitive assessments, 5) no other medical or psychiatric illness that could contribute importantly to dementia and no medical contraindication to lumbar puncture (LP). *APOE* genotypes were obtained as described.[9]

Cognitive assessments were performed annually and included assignment of the CDR,[10,11] CDR–sum of boxes (CDR-SB),[12] and a 1.5-hour psychometric test battery.[11] Study participants had an average of 3 annual cognitive assessments. A CDR designation of 0 indicating no dementia characterizes individuals who are cognitively normal controls, while a CDR 0.5 and CDR 1 designation denotes very mild and mild dementia, respectively. Clinical diagnoses were made in accordance with standard criteria.[13,14] Individuals with CDR 0.5 or greater at baseline (n = 60) in this study all had a clinical diagnosis of AD.

A psychometric test battery assessing a broad spectrum of cognitive functions[11] was administered to all participants within 1 to 2 weeks of the annual assessment. Standardized test scores were averaged to form 4 composite scores. The episodic memory composite included the sum of the 3 free recall trials from the Selective Reminding Test,[15] associate learning subtest of the Wechsler Memory Scale (WMS),[16] immediate recall of the WMS Logical Memory, and Benton Visual Retention test. The semantic memory composite included the Information subtest from the Wechsler Adult Intelligence Scale (WAIS),[17] Boston Naming Test,[18] and Animal Naming.[18] The working memory composite included WMS Mental Control, Digit Span Forward and Digit Span Backward, and Letter Fluency for S and P.[19] The visuospatial composite included the WAIS Block Design, Digit Symbol subtests, and Trail-making tests A and B.[20] The global psychometric composite score used was prorated based on other tests used to generate the original composite score because of changes in the psychometric test battery across the study period (e-Methods on the *Neurology*® Web site at www.neurology.org).

The reference (normative) group used to standardize most of the tests prior to forming the composites consisted of 310 participants (mean [SD]; age, 74.5 years [8.6]; education, 14.8 years [3.2]) who were enrolled as CDR 0, had at least one annual follow-up assessment, but never progressed to CDR > 0.[21] The means and standard deviations of 3 measures (Selective Reminding Test, Animal Naming, Trail Making B) not included in that report were based on the same robust sample but with slightly smaller sample sizes because these 3 tests were added to the battery after its initiation (e-Methods).

Data from a well-characterized cohort of cognitively normal controls (CDR 0; n = 211) enrolled at the WU-ADRC, who were included in a previous study,[8] are reported here to demonstrate differences in baseline CSF biomarker and psychometric characteristics between individuals with AD and controls.

Standard protocol approvals, registration, and patient consents. Studies were approved by the local ethical review board and the Human Studies Committee at Washington University. Informed consent was obtained from all participants.

CSF collection, processing, and assessment. CSF samples (20–30 mL) were collected from all participants and analyzed for total tau, p-tau181, Aβ42 (Innotest, Innogenetics, Ghent, Belgium),[22] and CSF Aβ40[23] by enzyme-linked immunosorbent assays as described. CSF samples were analyzed for VILIP-1 by a microparticle-based immunoassay (Erenna, Singulex, CA).

In vivo amyloid imaging. In vivo amyloid imaging is described in e-Methods.

Statistical analyses. The primary aim of the study is to determine whether CSF biomarkers/ratios predict annual change in CDR-SB, global, episodic memory, semantic memory, working memory, or visuospatial composite scores over the follow-up period. For this purpose, we used mixed linear models (PROC MIXED; SAS Institute Inc.) that specified a random subject-specific intercept and a random subject-specific slope. These models allow for heterogeneity among subjects in baseline values and rates of change, and account for correlation among repeated measures on the same subject. Analyses were adjusted for age, education, gender, *APOE* ϵ4 genotype, and baseline dementia severity (i.e., longitudinal CDR-SB models were adjusted for baseline global scores and global or individual composite models were adjusted for baseline CDR-SB to avoid the issue of circularity).

First, we examined whether CSF biomarkers/ratios, as continuous measures, predicted rates of cognitive decline over the follow-up period. CSF biomarker/ratio measures were standardized to z scores prior to analyses. Estimated effects of CSF biomarkers/ratios on annual change in cognitive measures are reported as β. Analyses were then repeated for CSF biomarkers/ratios as categorical variables (dichotomized at the 33rd or 66th percentile value) to determine whether there were significant differences in rates of cognitive decline between individuals in the upper tercile vs those in the lower 2 terciles for each CSF biomarker/ratio (or the lower tercile vs the upper 2 terciles for Aβ42). Baseline cognitive assessments were the closest assessments prior to the time of the LP. Statistical significance was defined as $p < 0.05$ (e-Methods).

RESULTS

Baseline characteristics of study participants. Sixty participants with a clinical diagnosis of AD and a CDR 0.5 (n = 46) or CDR 1 (n = 14) underwent LP and had at least 1 follow-up annual clinical assessment. Mean duration of follow-up was 2.6 years (range 0.9–6.9 years). Table 1 summarizes demographic, psychometric, and CSF biomarker variables at the baseline clinical assessment (median

Table 1 Baseline demographic, genotype, psychometric, and CSF biomarker characteristics of study participants with very mild (CDR 0.5) and mild (CDR 1) AD[a]

Demographics	CDR 0 (n = 211)[b]	CDR 0.5 (n = 46)	CDR 1 (n = 14)	CDR 0.5 and 1 (n = 60)	*p* Value
Age at LP, y, mean (SE)	72.1 (0.49)	75.4 (0.94)	78.5 (1.6)	76.2 (0.82)	<0.0001*
Gender, F/M, n (% F)	129/82 (61)	27/19 (59)	9/5 (64%)	36/24 (60)	0.88
Education, y, mean (SE)	15.6 (0.2)	14.4 (0.45)	13.2 (0.94)	14.1 (0.41)	0.0008*
APOE ε4 genotype, n ε4+/ε4− (% ε4+)[c]	62/149 (29)	29/17 (63)	10/4 (71%)	39/21 (65)	<0.0001*
Duration of follow up, y, mean (SE)	2.81[d] (0.13)	2.62 (0.26)	2.69 (0.46)	2.64 (0.22)	0.48
No. PiB+/PiB−[e] (% PiB+)	36/95 (27)	8/4 (67)	3/0 (100)	11/4 (73)	0.0007*
Baseline psychometric assessments[d]					
CDR-SB, mean (SE)	0.03 (0.01)	2.4 (0.21)	5.3 (0.35)	3.0 (0.24)	<0.0001*
MMSE, mean (SE)	29.0 (0.09)	25.8 (0.46)	24.1 (0.75)	25.4 (0.40)	<0.0001*
Episodic memory composite, mean (SE)	0.17 (0.06)	−1.48 (0.14)	−2.45 (0.17)	−1.70 (0.12)	<0.0001*
Semantic memory composite, mean (SE)	0.09 (0.06)	−0.86 (0.16)	−2.03 (0.23)	−1.12 (0.15)	<0.0001*
Working memory composite, mean (SE)	0.14 (0.05)	−0.40 (0.10)	−0.85 (0.21)	−0.50 (0.10)	<0.0001*
Visual spatial composite, mean (SE)	0.37 (0.06)	−0.62 (0.12)	−1.38 (0.32)	−0.78 (0.12)	<0.0001*
Global psychometric composite, mean (SE)	0.20 (0.04)	−0.78 (0.09)	−1.65 (0.14)	−0.97 (0.09)	<0.0001*
Baseline CSF biomarker measures					
VILIP-1, pg/mL, mean (SE)	396 (10)	526 (28)	568 (61)	536 (26)	<0.0001*
tau, pg/mL, mean (SE)	295 (11)†	575 (42)	577 (65)	576 (35)	<0.0001*
p-tau181, pg/mL, mean (SE)	54 (2)†	90 (7)	84 (11)	89 (6)	<0.0001*
Aβ42, pg/mL, mean (SE)	615 (17)‡	384 (23)	333 (19)	372 (18)	<0.0001*
tau/Aβ42, mean (SE)	0.60 (0.04)‡	1.68 (0.14)	1.85 (0.29)	1.72 (0.12)	<0.0001*
p-tau181/Aβ42, mean (SE)	0.11 (0.01)‡	0.26 (0.02)	0.27 (0.05)	0.27 (0.02)	<0.0001*
VILIP-1/Aβ42, mean (SE)	0.74 (0.03)‡	1.57 (0.11)	1.77 (0.20)	1.62 (0.09)	<0.0001*

Abbreviations: Aβ42 = amyloid-beta 1–42; AD = Alzheimer disease; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating–sum of boxes; LP = lumbar puncture; MMSE = Mini-Mental State Examination; p-tau181 = tau phosphorylated at threonine 181; PiB = Pittsburgh compound B; VILIP-1 = Visinin-like protein-1.

[a] Student *t* tests or χ^2 tests were used to compare demographic, psychometric, and CSF biomarker characteristics between controls (CDR 0) and individuals with AD (combined CDR 0.5 and CDR 1 cohorts). Better cognitive functioning is indicated by lower scores on the CDR-SB and higher psychometric composite scores.

[b] These values are from a cohort of cognitively normal individuals (CDR 0) from a previous study[8] and are included here for comparison.

[c] The *APOE* ε4+ genotype was defined by the presence of at least one *APOE* ε4 allele.

[d] Of the 211 cognitively normal individuals (CDR 0) who underwent LP in the previous study,[8] 164 individuals were followed longitudinally and had more than one annual cognitive assessment. Baseline cognitive measures reported herein represent baseline cognitive measures for the subset of cognitively normal individuals who had longitudinal cognitive assessments (n = 164).

[e] Of the 60 individuals with AD in this study, 15 individuals underwent PET-PiB, including individuals with CDR 0.5 (n = 12) and CDR 1 (n = 3). Of the 211 cognitively normal individuals (CDR 0) included here for comparison, 131 individuals underwent PET-PiB.

* $p < 0.05$.

† n = 201.

‡ n = 200.

interval, 3.4 months from the LP) for individuals with AD and controls without dementia. Individuals in the CDR 0.5 and CDR 1 cohorts exhibited the typical CSF biomarker phenotype of AD with elevated mean levels of tau and p-tau181 and lower levels of Aβ42. Baseline CSF VILIP-1 and VILIP-1/Aβ42 levels were higher in AD than in controls. Compared to controls, individuals with AD had higher CDR-SB scores, and lower global, episodic memory, semantic memory, working memory, and visuospatial composite scores at the time of the baseline assessment.

No correlations were observed between CSF biomarkers/ratios and cognitive measures at baseline (table e-1). Baseline CSF biomarker measures did not correlate with age or years of education, and did not differ by gender (e-Results).

Correlations between baseline CSF biomarker measures and subsequent change in CDR-SB and global composite scores. We examined whether baseline CSF biomarker measures (as continuous variables) predicted annual change in CDR-SB and global composite scores over the follow-up period in the

Table 2 CSF biomarker measures as predictors of cognitive decline in individuals with very mild (CDR 0.5) and mild (CDR 1) AD[a]

	Clinical or psychometric test score					
CSF biomarker	CDR-SB	Global psychometric composite	Episodic memory composite	Semantic memory composite	Working memory composite	Visual spatial composite
VILIP-1	0.33	−0.13	−0.17	−0.08	−0.02	0.03
	0.0007*	0.0001*	<0.0001*	0.0090†	0.70	0.46
tau	0.29	−0.12	−0.15	−0.07	−0.04	−0.002
	0.0012†	0.0004*	<0.0001*	0.0127‡	0.45	0.95
p-tau181	0.27	−0.11	−0.13	−0.06	−0.02	0.003
	0.0041†	0.0006*	0.0009*	0.0458‡	0.76	0.91
Aβ42	−0.23	0.09	0.07	0.10	0.01	0.09
	0.0229‡	0.0189‡	0.0950	0.0001*	0.92	0.19
tau/Aβ42	0.27	−0.13	−0.15	−0.08	−0.05	−0.03
	0.0010†	<0.0001*	<0.0001*	0.0015†	0.34	0.65
p-tau181/Aβ42	0.25	−0.13	−0.13	−0.07	−0.03	−0.03
	0.0026†	<0.0001*	<0.0001*	0.0130‡	0.64	0.37
VILIP-1/Aβ42	0.28	−0.14	−0.15	−0.08	−0.03	−0.02
	0.0001*	<0.0001*	<0.0001*	0.0016†	0.59	0.82
Aβ40	0.12	−0.05	−0.07	0.001	−0.04	0.05
	0.31	0.22	0.12	0.98	0.56	0.48

Abbreviations: Aβ42 = amyloid-beta 1–42; AD = Alzheimer disease; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating–sum of boxes; p-tau181 = tau phosphorylated at threonine 181; VILIP-1 = Visinin-like protein-1.

[a] In these analyses, CSF biomarker measures were standardized to *z* scores and examined as continuous variables. The top value represents the estimated effect (β) and the bottom value represents the *p* values for CSF biomarker/ratio measures (examined as continuous variables) as predictors of the annual change in cognitive measures in the combined (CDR 0.5 and CDR 1) cohort (n = 60). The given β value for a CSF biomarker/ratio reflects the difference in annual change in a cognitive measure per standardized biomarker unit. Analyses were adjusted for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity (i.e., longitudinal CDR-SB models were adjusted for baseline global composite scores, and global or individual composite models were adjusted for baseline CDR-SB).

* $p < 0.001$.

† $p < 0.01$.

‡ $p < 0.05$.

AD cohort (n = 60). Analyses were adjusted for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity. The average adjusted rate of cognitive decline (slope ± SE) in the AD cohort was 1.06 ± 0.12 boxes/year in CDR-SB, and −0.28 ± 0.05 points/year in global scores.

Baseline CSF VILIP-1 and VILIP-1/Aβ42 predicted annual change in CDR-SB and global scores over the follow-up period. With the exception of CSF Aβ40, all other CSF biomarkers/ratios predicted annual change in CDR-SB and global scores over the follow-up period. Table 2 summarizes the estimated effects (β) (top values) and *p* values (bottom values) for CSF biomarkers/ratios as predictors of annual change in CDR-SB and global scores.

Analyses were then performed for CSF biomarker measures as categorical variables (adjusting for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity). Individuals in the AD cohort (n = 60) were divided into 3 terciles for each CSF biomarker measure (using the 33rd and 66th percentile values as cutoffs). Consistent with our previous results, CSF VILIP-1 and VILIP-1/Aβ42 levels in the upper tercile (corresponding to CSF VILIP-1 ≥560 pg/mL and VILIP-1/Aβ42 ≥1.75) predicted more rapid change in CDR-SB (slope ± SE, 1.61 ± 0.25 and 1.54 ± 0.20 boxes/year, respectively) than those in the lower 2 terciles (0.85 ± 0.14 and 0.77 ± 0.15 boxes/year, respectively). Similarly, CSF VILIP-1 and VILIP-1/Aβ42 levels in the upper tercile predicted more rapid change in global scores than those in the lower 2 terciles. Table 3 and figure e-1, A–D, summarize rates of cognitive decline in CDR-SB and global scores as a function of CSF biomarker terciles in the AD cohort.

We then examined the utility of CSF biomarkers in predicting cognitive decline in the CDR 0.5 and CDR 1 cohorts separately. Table 4 summarizes rates of cognitive decline in CDR-SB and global scores in the CDR 0.5 cohort as a function of CSF biomarker

Table 3 Rates of decline in CDR–sum of boxes, global psychometric composite scores, and episodic memory composite scores (per year) in individuals with AD (CDR 0.5 and CDR 1) as a function of CSF biomarker measures[a]

CSF biomarker[b]	Lower 2 terciles	Upper tercile	*p* Value[c]
Rates of decline in CDR–sum of boxes (per year) in AD			
VILIP-1	0.852 ± 0.143	1.610 ± 0.248	0.0077*
tau	0.828 ± 0.148	1.545 ± 0.227	0.0095*
p-tau181	0.819 ± 0.144	1.583 ± 0.233	0.0053*
tau/Aβ42	0.823 ± 0.146	1.534 ± 0.227	0.0078*
p-tau181/Aβ42	0.824 ± 0.145	1.550 ± 0.230	0.0071*
VILIP-1/Aβ42	0.770 ± 0.151	1.538 ± 0.197	0.0017*
	Upper 2 terciles	Lower tercile	
Aβ42	0.867 ± 0.163	1.310 ± 0.200	0.0559
Rates of decline in global psychometric composite scores (per year) in AD			
VILIP-1	−0.150 ± 0.053	−0.534 ± 0.079	0.0002†
tau	−0.181 ± 0.058	−0.475 ± 0.083	0.0036*
p-tau181	−0.188 ± 0.056	−0.485 ± 0.086	0.0039*
tau/Aβ42	−0.150 ± 0.050	−0.581 ± 0.077	<0.0001†
p-tau181/Aβ42	−0.150 ± 0.049	−0.594 ± 0.078	<0.0001†
VILIP-1/Aβ42	−0.112 ± 0.044	−0.615 ± 0.065	<0.0001†
	Upper 2 terciles	Lower tercile	
Aβ42	−0.206 ± 0.062	−0.417 ± 0.080	0.0376‡
Rates of decline in episodic memory composite scores (per year) in AD			
VILIP-1	−0.145 ± 0.058	−0.648 ± 0.090	0.0001†
tau	−0.182 ± 0.064	−0.590 ± 0.097	0.0005†
p-tau181	−0.193 ± 0.064	−0.594 ± 0.101	0.0008†
tau /Aβ42	−0.178 ± 0.060	−0.645 ± 0.100	<0.0001†
p-tau181/Aβ42	−0.178 ± 0.060	−0.659 ± 0.101	<0.0001†
VILIP-1/Aβ42	−0.148 ± 0.058	−0.674 ± 0.091	<0.0001†
	Upper 2 terciles	Lower tercile	
Aβ42	−0.278 ± 0.077	−0.404 ± 0.101	0.3246

Abbreviations: Aβ42 = amyloid-beta 1–42; AD = Alzheimer disease; CDR = Clinical Dementia Rating; p-tau181 = tau phosphorylated at threonine 181; VILIP-1 = Visinin-like protein-1.

[a] Mixed linear models were used to estimate rates of decline in CDR-SB, global psychometric composite scores, and episodic memory composite scores in the combined (CDR 0.5 and CDR 1) cohort over time as a function of CSF biomarker measures (adjusting for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity). In these analyses, CSF biomarkers were examined as categorical variables (dichotomized at the 33rd or 66th percentile) to compare rates of decline between individuals in the upper tercile vs those in the lower 2 terciles for CSF biomarker measures (or the lower tercile vs the upper 2 terciles for Aβ42).

[b] The 66th percentile cutoff values in the combined cohort (CDR 0.5 and CDR 1; n = 60) were 560 pg/mL, 607 pg/mL, 93 pg/mL, 1.90, 0.28, and 1.75, for VILIP-1, tau, p-tau181, tau/Aβ42, p-tau181/Aβ42, and VILIP-1/Aβ42, respectively. CSF Aβ42 values were dichotomized at the 33rd percentile value (295 pg/mL).

[c] *p* Values reflect whether CSF biomarker measures (dichotomized at the 33rd or 66th percentile value) significantly predict rates of cognitive decline in the combined cohort (adjusting for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity). Longitudinal CDR-SB models were adjusted for baseline global composite scores, and global or individual composite models were adjusted for baseline CDR-SB.

* $p < 0.01$.

† $p < 0.001$.

‡ $p < 0.05$.

terciles. In the CDR 0.5 cohort, CSF VILIP-1 or CSF VILIP-1/Aβ42 values in the upper tercile were associated with more rapid change in CDR-SB and global scores than those in the lower 2 terciles, respectively (figure 1). Similar results were seen in the CDR 1 cohort (table e-2 and e-Results).

Table 4 Rates of decline in CDR-sum of boxes, global psychometric composite scores, and episodic memory composite scores (per year) in individuals with very mild AD (CDR 0.5) as a function of CSF biomarker measures[a]

CSF biomarker[b]	Lower 2 terciles	Upper tercile	*p* Value[c]
Rates of decline in CDR-sum of boxes (per year) in very mild AD			
VILIP-1	0.762 ± 0.128	1.579 ± 0.262	0.0050*
tau	0.705 ± 0.133	1.524 ± 0.233	0.0023*
p-tau181	0.691 ± 0.129	1.594 ± 0.240	0.0008†
tau/Aβ42	0.669 ± 0.127	1.487 ± 0.210	0.0009†
p-tau181/Aβ42	0.680 ± 0.127	1.492 ± 0.216	0.0012*
VILIP-1/Aβ42	0.641 ± 0.117	1.501 ± 0.175	0.0001†
	Upper 2 terciles	Lower tercile	
Aβ42	0.780 ± 0.159	1.295 ± 0.200	0.0448‡
Rates of decline in global psychometric composite scores (per year) in very mild AD			
VILIP-1	−0.169 ± 0.048	−0.379 ± 0.091	0.0393‡
tau	−0.182 ± 0.050	−0.374 ± 0.089	0.0504
p-tau181	−0.170 ± 0.049	−0.373 ± 0.090	0.0481‡
tau/Aβ42	−0.118 ± 0.041	−0.478 ± 0.072	<0.0001†
p-tau181/Aβ42	−0.120 ± 0.042	−0.463 ± 0.070	<0.0001†
VILIP-1/Aβ42	−0.108 ± 0.040	−0.488 ± 0.069	<0.0001†
	Upper 2 terciles	Lower tercile	
Aβ42	−0.140 ± 0.052	−0.350 ± 0.069	0.0152‡
Rates of decline in episodic memory composite scores (per year) in very mild AD			
VILIP-1	−0.129 ± 0.047	−0.494 ± 0.086	0.0002†
tau	−0.140 ± 0.051	−0.457 ± 0.086	0.0015*
p-tau181	−0.153 ± 0.052	−0.470 ± 0.094	0.0032*
tau/Aβ42	−0.136 ± 0.048	−0.528 ± 0.092	0.0002†
p-tau181/Aβ42	−0.136 ± 0.047	−0.539 ± 0.093	0.0001†
VILIP-1/Aβ42	−0.116 ± 0.046	−0.567 ± 0.086	0.0001†
	Upper 2 terciles	Lower tercile	
Aβ42	−0.138 ± 0.062	−0.367 ± 0.073	0.0171‡

Abbreviations: Aβ42 = amyloid-beta 1-42; AD = Alzheimer disease; CDR = Clinical Dementia Rating; p-tau181 = tau phosphorylated at threonine 181; VILIP-1 = Visinin-like protein-1.

[a] Mixed linear models were used to estimate rates of decline in CDR-SB, global psychometric composite scores, and episodic memory composite scores in the CDR 0.5 cohort over time as a function of CSF biomarker measures (adjusting for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity). In these analyses, CSF biomarkers were examined as categorical variables (dichotomized at the 33rd or 66th percentile) to compare rates of decline between individuals in the upper tercile vs those in the lower 2 terciles for CSF biomarker measures (or the lower tercile vs the upper 2 terciles for Aβ42).

[b] The 66th percentile cutoff values for the CDR 0.5 cohort (n = 46) were 563 pg/mL, 634 pg/mL, 95 pg/mL, 1.93, 0.28, and 1.74 for VILIP-1, tau, p-tau181, tau/Aβ42, p-tau181/Aβ42, and VILIP-1/Aβ42, respectively. CSF Aβ42 values were dichotomized at the 33rd percentile value (299 pg/mL).

[c] *p* Values reflect whether CSF biomarker measures (dichotomized at the 33rd or 66th percentile value) significantly predict rates of decline in the CDR 0.5 cohort (adjusting for age, education, gender, *APOE* ε4 genotype, and baseline dementia severity). Longitudinal CDR-SB models were adjusted for baseline global composite scores, and global or individual composite models were adjusted for baseline CDR-SB.

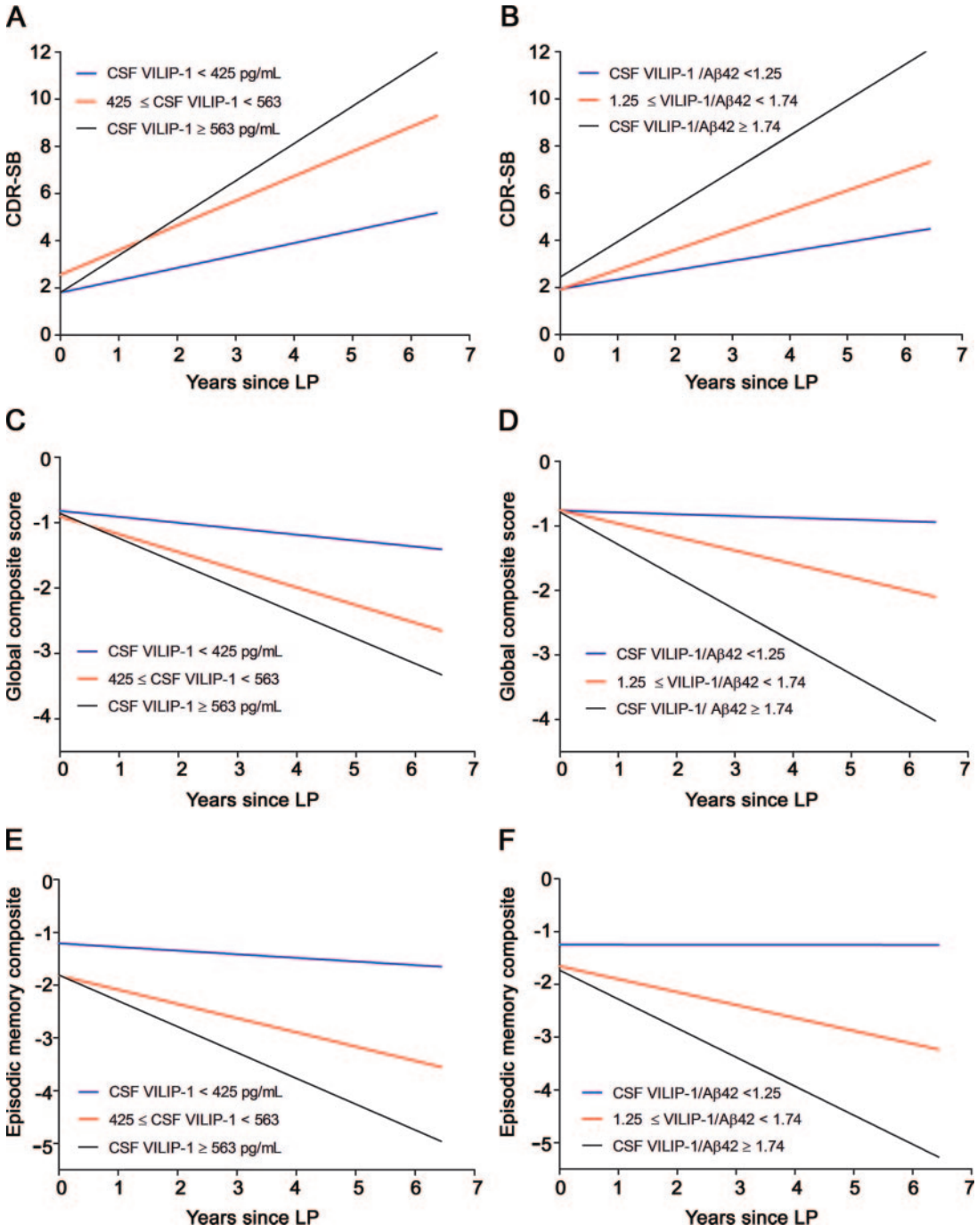
* $p < 0.01$.

† $p < 0.001$.

‡ $p < 0.05$.

We then examined the utility of CSF biomarker measures in predicting annual change in individual composite scores. CSF VILIP-1, tau, p-tau181, tau/Aβ42, p-tau181/Aβ42, and VILIP-1/Aβ42 predicted change in episodic and semantic memory scores, but not working memory or visuospatial

Figure 1 Rates of decline in (A and B) Clinical Dementia Rating–sum of boxes (CDR-SB), (C and D) global psychometric composite scores, and (E and F) episodic memory composite scores as a function of CSF VILIP-1 and VILIP-1/Aβ42 terciles in very mild Alzheimer disease (CDR 0.5)



Mixed linear models were used to estimate rates of decline in CDR-SB (A and B), global psychometric composite scores (C and D), and episodic memory scores (E and F) over time in the CDR 0.5 cohort as a function of CSF VILIP-1 and VILIP-1/Aβ42. The slope and intercept for each of the 3 terciles of CSF VILIP-1 and CSF VILIP-1/Aβ42 are plotted. Adjusted rates of cognitive decline in the upper, middle, and lower terciles of VILIP-1 values were 1.58, 1.05, 0.52 boxes/year (respectively) for CDR-SB, −0.38, −0.27, and −0.09 points/year (respectively) for global composite scores, and −0.49, −0.27, and −0.07 points/year (respectively) in episodic memory scores. Adjusted rates of cognitive decline in the upper, middle, and lower terciles of VILIP-1/Aβ42 values were 1.50, 0.84, and 0.40 boxes/year (respectively) in CDR-SB, −0.49, −0.21, and −0.03 points/year (respectively) in global composite scores, and −0.57, −0.25, and −0.001 points/year (respectively) in episodic memory scores. LP = lumbar puncture.

scores in the combined cohort (table 2). Individuals in the upper tercile of VILIP-1 or VILIP-1/Aβ42 values declined more rapidly in episodic memory scores than individuals in the lower 2 terciles. Similar results were seen in the CDR 0.5 and CDR 1 cohorts when examined separately. Table 3 and figure e-1, E–F, summarize rates of decline in episodic memory as a function of CSF biomarker terciles in the AD cohort. Table 4 and figure 1, E–F, summarize rates of decline in episodic memory in the CDR 0.5 cohort, and table e-2 in the CDR 1 cohort.

DISCUSSION VILIP-1 is a highly expressed neuronal calcium-sensor protein,[5] which has demonstrated utility as a neuronal injury marker in brain injury models and gene-array analyses.[6] Increased CSF VILIP-1 levels and altered expression patterns of VILIP-1 in AD may reflect the selective vulnerability of VILIP-1-expressing neurons to calcium-mediated neurodegeneration in the presence of AD pathology.[24] VILIP-1 is detected in dystrophic neurites and in close association with amyloid plaques and neurofibrillary tangles (NFT), but does not appear to be a component of NFT.[8,24] CSF VILIP-1 levels correlate with whole brain and regional atrophy in early symptomatic AD, and with amyloid load in cognitively normal individuals.[8] Together, these findings support the potential utility of CSF VILIP-1 as a biomarker surrogate for neurodegeneration in AD.[8]

We have previously shown that CSF VILIP-1 levels can predict future cognitive impairment in cognitively normal individuals similarly to tau and p-tau181 over a 2- to 3-year follow-up period.[8] We here investigate the utility of CSF VILIP-1 in predicting rates of cognitive decline in a well-characterized cohort of cognitively impaired individuals with very mild and mild AD who were followed for 2–3 years. Our results suggest that CSF VILIP-1, alone or in combination with Aβ42 (VILIP-1/Aβ42), predicts rates of cognitive decline over this follow-up period. The clear and ordered separation of the rates of cognitive decline in CDR-SB and global scores among the 3 terciles for CSF VILIP-1 and VILIP-1/Aβ42, and the ability of these markers to predict rates of decline when examined as continuous measures, highlight their predictive ability independently of the cutoff values proposed in this study.

Importantly, CSF VILIP-1 and other CSF markers of AD pathology predicted annual cognitive decline even after adjusting for baseline cognitive performance. Since the rate of cognitive decline in AD is not linear and may differ by disease stage,[25] these findings are particularly notable and suggest that CSF biomarkers, including VILIP-1, may complement information provided by clinical assessments in guiding prognostic and therapeutic decisions in clinical practice or in trials of disease-modifying therapies.

Consistent with previous reports,[26] CSF tau, p-tau181, tau/Aβ42, and p-tau181/Aβ42 predicted rates of future cognitive decline over this follow-up period. As previously described,[27] CSF Aβ42 levels appeared to be a less significant predictor of cognitive decline in our cohort than CSF tau, p-tau181, and VILIP-1; low CSF Aβ42 levels were associated with higher rates of progression in the CDR 0.5 but not in the CDR 1 cohort. While the initial decrease in CSF Aβ42 levels is thought to occur a decade or longer prior to the onset of cognitive impairment,[1,2,28,29] once they are low,[22] CSF Aβ42 levels remain relatively stable for years in impaired and unimpaired individuals.[30,31] Conversely, following the earliest signs of cognitive impairment, progressive increase in NFT pathology and progressive neuronal loss on a background of substantial Aβ accumulation correlates with further cognitive decline and disease progression in AD.[28] Therefore, it is likely that this new low set point for Aβ42 can predict rates of decline over the 2- to 3-year follow-up period in the CDR 0.5 cohort, but not in more advanced disease stages, while CSF VILIP-1 (reflective of neuronal/synaptic degeneration) and tau/p-tau181 (reflective of NFT formation) correlate more closely with disease progression in the very mild (CDR 0.5) and mild (CDR 1) stages.

Our findings support the notion that substantial neuronal loss/neurodegeneration is present by the time the earliest signs of cognitive impairment appear, and correlates well with clinical disease progression in AD.[28,32] CSF Aβ42 and tau levels each predominantly reflect a specific AD pathology, and do not appear to change considerably with clinical disease progression.[30,31] Conversely, neuronal/synaptic loss likely reflects the cumulative outcome of different pathologic substrates. Therefore, CSF markers which capture neuronal loss/neurodegeneration, such as VILIP-1, may offer predictive value for future cognitive decline that is at least comparable to that of CSF markers of tau and amyloid. Theoretically, such markers may also demonstrate response to a treatment that decreases neurodegeneration independently of changes to Aβ42 and tau. In the cohort studied herein, VILIP-1 predicted future cognitive decline over the follow-up period at least as well as tau, p-tau181, and Aβ42. Our results suggest trends for a potentially superior predictive performance for VILIP-1 to tau or Aβ42 in the AD cohort over a 2- to 3-year follow-up period (tables 2 and 3). However, while VILIP-1 is similar to tau in its prognostic ability, we cannot say for sure at this time whether VILIP-1 is better than tau in this regard from our

current data. It will be important to study larger cohorts of individuals with longer durations of follow-up, and from different centers, to further evaluate the predictive performance of VILIP-1 in comparison to other markers of AD pathology.

Our study is similar to previous studies examining rates of decline in AD,[26,27,32] but differs from other studies in which dichotomous outcomes of conversion/no conversion from very mild (CDR 0.5 or MCI) to mild (CDR 1) AD were examined.[33,34] There is a great deal of variability in baseline cognitive scores (CDR-SB or psychometric test scores) among individuals with AD within the same CDR category, and in the degree of further impairment required for the transition between global CDR categories. The use of outcome measures with more gradation to measure cognitive decline (e.g., CDR-SB, psychometric test scores) takes such interindividual variability into consideration, and likely provides better insight into the biological or radiologic correlates of disease progression among different individuals over time.

Consistent with previous reports,[21,35,36] our CDR 0.5 cohort showed impairment in baseline episodic memory compared to controls, with less severe impairment in semantic memory, working memory, and visuospatial composite scores. Clinicopathologic and radiologic studies suggest that hippocampal and parahippocampal regions mediate episodic memory functions,[35,37] while polar temporal, inferior temporal, and anterior fusiform regions are implicated in semantic memory.[38] Our observation that VILIP-1 levels correlate with decline in episodic and semantic memory is consistent with early involvement of medial temporal and fusiform regions (respectively) by AD pathology,[39] and with our findings that CSF VILIP-1 levels correlate with atrophy of these regions in early AD.[8]

Together, these findings highlight the potential utility of CSF VILIP-1 in guiding trial design, outcome assessment, and prognostic decisions in clinical trials of disease-modifying therapies and clinical settings. The incorporation of CSF VILIP-1, along with other CSF biomarkers, into such trials may assist in the accurate selection of homogeneous study participants, by limiting enrollment to individuals who are likely to progress within the study period based on their CSF biomarker values. Our study is limited by the relatively few individuals with mild dementia, and by the short duration of follow-up. Validation of these findings in larger populations of individuals with mild to moderate AD and with longer durations of follow-up will be of interest in the future. The evaluation of a larger number of CSF samples using the VILIP-1 immunoassay utilized in this study and efforts to standardize this assay across different centers will be the focus of future studies, similar to what has been or is currently being done for tau and Aβ42 (e-Comment).

AUTHOR CONTRIBUTIONS

Dr. Tarawneh: study design, data acquisition, analysis and interpretation of data, statistical analyses, drafting manuscript. Dr. Lee: study design, analysis and interpretation of data, revising manuscript for medical content. Dr. Ladenson: study design, analysis and interpretation of data, obtaining funding, revising manuscript for medical content, contribution of vital reagents/tools. Dr. Morris: study design, obtaining funding, revising manuscript for medical content, contribution of vital reagents/tools. Dr. Holtzman: study design, analysis and interpretation of data, drafting and revising manuscript for medical content, contribution of vital reagents/tools, study coordination, obtaining funding.

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DISCLOSURE

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