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Biomarkers of Cognitive Impairment: Brain Cortical Thickness, Volumetrics and Cerebrospinal Fluid

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Abstract

In Alzheimer's disease (AD), association of cognition with disease biomarkers is important for accurate diagnosis, prognosis and staging. We studied the value of cerebrospinal fluid (CSF), cortical thickness (CT), and volume (V) measures (in isolation & combination) to predict cognitive ability, as well as cognitive status, in a cross-sectional study of data from Alzheimer's Disease Neuroimaging Initiative (ADNI). Cognitive status was measured by Mini Mental State Exam (MMSE). Results show that combining biomarkers allows more accurate AD diagnosis. Specifically, combining CSF, CT, and V measures seems promising. In isolation, CSF levels show significant but weak associations with MMSE. Aβ 1–42 is associated with Mild Cognitive Impairment. CT and V measures of hippocampus and entorhinal cortex are strongly associated with Alzheimer's Disease diagnosis and with ruling out the disease.

Keywords

Alzheimer's Disease; Biomarkers; Cortical Thickness; Volumetric; CSF

1. Introduction

Brain changes related to Alzheimer's disease (AD) exist years before manifestation of any cognitive decline¹. Mild cognitive impairment (MCI) is impairment in cognition with preserved independence and functional abilities. MCI is considered a risk factor for dementia, however, not all MCI conditions are due to AD pathology. While ultimate diagnosis of AD is made at autopsy², more accurate in vivo diagnosis can be achieved by

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combining biomarkers in combination with clinical tests and history³. Understanding how combinations of biomarkers improve diagnosis and assessment of the impact of novel therapeutics is important.

Proteins such as Tau, Abeta1–42, PTau181P, which are aggregated as neurofibrillary tangles and amyloid plaques and are also present in the cerebrospinal fluid (CSF), are considered as AD biomarkers⁴. Decreased levels of CSF Abeta42 and increased levels of Tau and phosphorylated Tau (p-Tau) are considered biomarkers indicating underlying AD pathology⁵. Moreover, AD is associated with changes in brain structure, including changes to cortical thickness and cortical and subcortical volumes⁶. Specifically, reduced volume of hippocampus is accepted as an AD biomarker⁵.

While CSF and imaging biomarkers are frequently analyzed in isolation, the current study uses a well characterized dataset to test the utility of biomarkers both in isolation and in combination, in a large population, and a unique statistical approach. The aims are to 1) differentiate groups including AD, MCI, and healthy participants with normal cognitive status (NCS), and 2) assess relationship of imaging (CT & V) and fluid biomarker (CSF) with cognition.

2. Methods

2.1 Participants and Material

Here we present a cross sectional study on 822 individuals (M=77, SD=6.9) including healthy controls with NCS and patients diagnosed with MCI or AD. Data used in the preparation of this article were ADNI 1, obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Diagnoses were made following ADNI protocol (adni.loni.usc.edu). NCS Participants showed no sign of depression, mild cognitive impairment or dementia. MCI participants reported a subjective memory concern despite maintaining daily activities, and their performance on Wechsler Memory Scale Logical Memory II. Participants would be labeled as AD if they met the NINCDS/ADRDA criteria for probable AD⁷.

We used the Mini Mental State Exam (MMSE) data to assess overall cognition. CSF levels of total Tau, Abeta1–42, and PTau181P proteins were analyzed and structural measures of brain regions of interest (ROI) were computed using freesurfer version 4.3, downloaded on April 18th, 2016 (<https://surfer.nmr.mgh.harvard.edu/>). Regions were selected to include currently accepted biomarkers and regions known to be affected early in the AD process⁸. These measures included CT of 38 regions (ROIs) as well as total gray matter. ROIs were the left and the right hippocampus, ACC, insula, inferior parietal cortex, middle frontal cortex, inferior temporal cortex, pre-central cortex, post-central cortex, caudate-middle frontal cortex, and frontal poles, inferior frontal gyrus, superior frontal gyrus, inferior

parietal gyrus, inferior temporal gyrus, middle temporal gyrus, post-central cortex, caudate-middle frontal cortex, entorhinal cortex, precuneus, and fusiform. Also, the volume measures of (V) of 20 ROIs were the right and the left inferior parietal, entorhinal cortex, middle temporal gyrus, temporal lobe, thalamus, hippocampus, middle temporal gyrus, putamen, caudate, and amygdala.

2.2 Data Analysis

Pearson's correlations were calculated to measure the association between CSF protein levels, CT of brain ROIs and Vs of brain ROIs with MMSE scores. To correct for the probability of accepting null hypotheses due to multiple comparisons, Family-Wise Error Rate Bonferroni correction was used to adjust p values. For the whole population, regression models including every individual predictor were used to determine the variables explaining the highest variance of outcome of MMSE. All variables that explained more than 10% of variance were entered in separate stepwise regression models: Specifically, a linear regression model involving the CSF variables, another model involving CT variables and a third model including volumetric variables. Using Variable Inflation Factor (VIF), collinearity was checked among variables. Predictors that showed collinearity were not included in the regression model. Predictors that could significantly contribute in explaining the variance of outcome of MMSE were put in a single stepwise linear regression model. A forward stepwise logistic binary analysis was performed with the variables explaining the variance of outcome of cognitive impairment, to estimate prediction of correct diagnosis (AD, MCI, and NCS).

Table I. Predictors of the MMSE scores including CT and V of ROIs, as well as CSF proteins. Results of individual regression models, and selection of ROIs above the cut-off.

3. Results

Individual regressions showed that CSF Tau, A β 1–42 and pTau181P were significantly associated with MMSE and explained 7%–11% of its variance. Regression models combining CT and V variables, showed that V of the left hippocampus and both entorhinal cortices and CT of the right middle temporal gyrus, as well as the left entorhinal cortex and the inferior parietal gyrus explained about 20% of variance in MMSE. Stepwise regression of a model including CSF A β 1–42, as well as the above regions explained 50% of variance in MMSE. Table II summarizes the association of CSF proteins, ROI's V and CT with MMSE.

CSF A β 1–42 was also associated with MCI diagnosis. A β 1–42, volume of the right entorhinal cortex and the CT of the left inferior parietal gyrus and the entorhinal cortex were associated with AD diagnosis. Normal levels of CSF A β 1–42 Tau combined with no structural changes to the temporal lobes confirmed normal status.

Table II summarizes the association of CSF proteins, ROI's V and CT with cognitive impairment.

4. Discussion

Combining imaging and CSF results created a more sensitive biomarker associate of cognitive function, validating previous reports⁴. The importance of biomarkers for diagnosis was also confirmed. Higher level of CSF A β 1–42 showed association with MCI (Table II). It has been argued that a positive CSF A β 1–42 without any evidence of neuroanatomical injury has an intermediate likelihood that MCI is due to AD⁵. This is while lower levels of CSF A β 1–42 are used to differentiate AD from other dementia^{3, 5}. Consistent with the literature⁴, combinations of CSF and MRI biomarkers offer stronger support for accurate diagnosis, as compared to individual biomarkers. CSF A β 1–42 levels, combined with CT and V measures of hippocampus and entorhinal cortices were strongly associated with AD diagnosis (Table II). These results are consistent with previous studies on diagnostic biomarkers studies³: Normal levels of CSF A β 1–42 and Tau and normal volume of the left entorhinal and the hippocampus as well as normal thickness of the right middle temporal gyrus significantly were associated with normal cognitive status (Table II).

In line with previous studies⁹, in isolation, various CSF levels showed significant but weak associations with MMSE scores, A β 1–42 showing the strongest association (See Table I). Imaging biomarkers also related to cognition: temporal lobe measures, including the hippocampus and the entorhinal cortex, as well as the parietal gyrus were associated with MMSE (Table I). Changes to these regions are known to be the early signs of cognitive impairment¹⁰. Given the early course of Alzheimer's disease in these regions impacts new memory formation, these results were expected.

This study showed that combined CSF, CT, and V measures offer promise for early AD diagnosis and tracing of cognitive decline in well-defined cohorts. However, their ability to predict outcome needs to be tested prospectively in typical clinical population and with autopsy confirmed AD pathology. Further, CSF measures are invasive. More research is required to reach noninvasive but rapid, inexpensive and reliable biomarkers.

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Table I

Association of cerebrospinal fluid (CSF) proteins, region of interest (ROI)'s volume and cortical thickness with Mini Mental State Exam (MMSE).

MMSE	Predictors	Variance of outcome
CSF	Tau	$R^2=0.07$, $\beta= .28$, $F(1,407)=35.012$, $p<.000$
	Abeta1-42	$R^2 =0.11$, $\beta= .33$, $F(1,412)=51.4$, $p<.000$
	PTau181P	$R^2=0.07$, $\beta= -.27$, $F(1,413)=33.51$, $p<.000$
ROIs' volume	L hippocampus	$R^2= 0.205$, $\beta= .453$, $F(1,818)=210.7$, $p<.000$
	L entorhinal cortex	$R^2= 0.194$, $\beta= .382$, $F(1,110)=18.804$, $p<.000$
	R entorhinal cortex	$R^2= 0.194$, $\beta= .403$, $F(1,818)=159.05$, $p<.000$
ROIs' CT	R middle temporal gyrus	$R^2= 0.17$, $\beta= .417$, $F(1,818)=172.12$, $p<.000$
	L entorhinal cortex	$R^2=0.21$, $\beta= .160$, $F(1,818)=21.58$, $p<.000$
	L inferior parietal gyrus	$R^2=0.21$, $F(1,818)=21.58$, $\beta= .160$, $p<.000$
All predictors	Abeta1-42	$R^2=0.5$, $F(5, 408)=106.96$, $p<.000$
	L hippocampus	
	L entorhinal cortex	
	R entorhinal cortex	
	R middle temporal gyrus	
	L entorhinal cortex	
	L inferior parietal gyrus	

Table II

Association of cerebrospinal fluid (CSF) proteins, region of interest (ROI)'s volume and cortical thickness with Cognitive Status (CS).

CS	Predictors	% Correctly predicted	Chi square, df Cox & Snell R square, Nagelkerke R square B, SE, ExpB
MCI	A β 1–42,	55.7 %,	$X^2=5.64$, df= 1
	Constant	p< 0.01	Cox & Snell R ² = 0.014, Nagelkerke R ² = 0.018
			B=–0.004, SE=0.002, ExpB=0.996
			B=0.617, SE=0.317, ExpB=1.85
AD	A β 1–42,	80.4%,	$X^2=112.20$, df= 4
	V of R entorhinal cortex	p<0.0001	Cox & Snell R ² = 0.240, Nagelkerke R ² = 0.357
	CT of L inferior parietal gyrus,		B=–0.01, SE=0.003, ExpB=0.990
	CT of L entorhinal cortex		B=–1.207, SE=0.319, ExpB=0.299
	Constant		B=–2.562, SE=0.690, ExpB=0.077
			B=–0.001, SE=0.0001, ExpB=0.999
NCS	Tau	79.5%,	$X^2=150.75$, df= 5
	A β 1–42,	p<0.001	Cox & Snell R ² = 0.308, Nagelkerke R ² = 0.444
	V of L entorhinal cortex		B=–0.01, SE=0.004, ExpB=0.990
	V of L hippocampus		B=–0.009, SE=0.003, ExpB=1.009
	CT of R middle temporal gyrus		B=0.977, SE=0.360, ExpB=2.655
	Constant		B=–0.001, SE=0.0001, ExpB=1.001
			B=1.871, SE=0.788, ExpB=6.497
			B=–13.320, SE=2.266, ExpB=0.0001