Alzheimer's & Dementia 10 (2014) 684-689

Limited agreement between biomarkers of neuronal injury at different stages of Alzheimer's disease

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Abstract New diagnostic criteria for Alzheimer's disease (AD) treat different biomarkers of neuronal injury as equivalent. Here, we quantified the degree of agreement between hippocampal volume on structural magnetic resonance imaging, regional glucose metabolism on positron emission tomography, and levels of phosphorylated tau in cerebrospinal fluid (CSF) in 585 subjects from all phases of the AD Neuroimaging Initiative. The overall chance-corrected agreement was poor (Cohen κ, 0.24–0.34), in accord with a high rate of conflicting findings (26%–41%). Neither diagnosis nor *APOE* ε4 status significantly influenced the distribution of agreement between the biomarkers. The degree of agreement tended to be higher in individuals with abnormal versus normal CSF β-amyloid ($A\beta_{1-42}$) levels. Prospective diagnostic criteria for AD should address the relative importance of markers of neuronal injury and elaborate a way of dealing with conflicting biomarker findings.

Keywords: Dementia; Agreement; Diagnostic criteria; Tau; FDG-PET; Hippocampal atrophy

1. Introduction

New diagnostic guidelines of the National Institute on Aging and the Alzheimer's Association (NIA-AA) have integrated biomarkers of Alzheimer's disease (AD) into the diagnostic algorithm for clinical research settings [1,2]—an important step toward early diagnosis and potential prevention of AD. Although the NIA-AA criteria rely on a conceptual model [3] and large body of empirical evidence, they make some implicit assumptions that need to be further evaluated [4]. One of them is that different biomarkers within the same category, amyloid accumulation or neuronal injury,

Panagiotis Alexopoulos and Laura Kriett contributed equally to the manuscript.

Conflict of interest: None.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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http://dx.doi.org/10.1016/j.jalz.2014.03.006

track the same pathomechanism. That is, the biomarkers within the same category are treated as equivalent to obtain a degree of certainty that the clinical symptoms of a given subject are caused by the AD pathophysiological process. In such a case, a high degree of agreement between the biomarkers would be expected. Studies on amyloid markers point to a good but still imperfect agreement [5–7]. Less clear are the interrelations between biomarkers of neural injury. A few prior studies on this topic included the imaging biomarkers only or were restricted to small samples [6,8,9]. Thus, the present study investigated the agreement between cerebrospinal fluid (CSF) phosphorylated tau (p-tau) levels, regional cerebral metabolism (MET) on positron emission tomography (PET) scans, and hippocampal volume (HIP) on structural magnetic resonance imaging (MRI) in 585 subjects from the AD Neuroimaging Initiative (ADNI). This multicenter setting is the ideal environment to study biomarker interrelations, providing a large sample size of subjects at different disease stages and ensuring uniform biomarker assessment procedures. Essentially, variance in operating procedures and measurement methods/assays critically affect clinical applicability of both imaging and CSF biomarkers [10,11].

2. Methods

The data used were obtained from the ADNI database at www.loni.ucla.edu/ADNI on July 31, 2013. The study was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives after extensive description of ADNI. Included were baseline data from elderly healthy subjects (HSs), subjects with so-called early mild cognitive impairment (eMCI) [12], and patients with MCI and probable AD from all phases of ADNI with available neuropsychological test results, *APOE* status, CSF proteins, ^{18}F-fluorodeoxyglucose (FDG) PET, and structural MRI scans (Table 1). For 113 participants, from whom no screening/baseline MRI scans were available, those acquired at the 3-month follow-up visit were included in the analyses.

Standardized biomarker acquisition and performance methods of ADNI are described at www.loni.ucla.edu/ADNI. Protocols of image and CSF analyses are reported in detail elsewhere [13–16]. In brief, the mean FDG count per subject was extracted from a composite region of interest on the basis of the AD-typical hypometabolic pattern [6,16]. Hippocampal volumes were extracted from structural MRI scans (1.5 T) using the FreeSurfer software http://surfer.nmr.mgh.harvard.edu [16]. Peptide concentrations were measured in CSF using aliquots obtained from the same vial at the same thaw [17]. *APOE* genotypes were determined using standard polymerase chain reaction methods [6]. To differentiate between normal and pathologic biomarker findings, we applied cutoffs that have been validated in previous ADNI publications [6,7,13,16,18] (Table 1).

To assess the association between different biomarkers, the percent agreement was derived, and chance-corrected agreement was calculated using kappa (κ) statistics. K $\leq$ 0.40 indicates poor, 0.41 to 0.60 moderate, 0.61 to 0.80 good, and $\geq$0.81 very good agreement [19]. Differences between diagnostic groups, between *APOE* ε4 carriers and noncarriers, and between patients with normal and abnormal CSF $A\beta_{42}$ levels (cutoff $\leq$192 pg/mL) [6,7,18] with regards to the distribution of agreement between the biomarkers were assessed with the chi-square test. In all analyses, a two-sided level of significance of 0.05 was applied.

Table 1
Description of the study sample

Variable	HS	eMCI	MCI	AD	All	Aβ (+)	Aβ (−)
N	156	189	164	76	585	308	277
Gender, female (%)	42.3	45	38.4	36.8	41.4	39.9	43.0
Age (y)	74.8 (5.5)	71.2 (7.5)	74.0 (7.4)	75.3 (8.6)	73.5 (7.3)	74.5 (6.9)	72.3 (7.6)
Education (y)	16.2 (2.8)	15.8 (2.6)	16.2 (2.8)	15.1 (3.4)	15.9 (2.9)	15.7 (2.9)	16.2 (2.8)
APOE ε4 carriers (%)	23.1	38.6	54.9	72.4	43.4	64.9	19.5
MMSE	29.0 (1.2)	28.4 (1.5)	27.4 (1.8)	23.4 (2.0)	27.6 (2.4)	26.9 (2.6)	28.5 (1.7)
CSF $A\beta_{1\text{-}42}$, pg/mL	224.6 (68.2)	230.9 (72.3)	168.9 (60.5)	143.5 (43.0)	200.5 (73.0)	140.8 (29.2)	266.8 (44.2)
AD-positive ($\leq$192 pg/mL) CSF $A\beta_{1\text{-}42}$ (%)	32.7	36.0	73.2	90.8	52.6	100	0
FDG-PET, relative counts	1.31 (0.11)	1.30 (0.12)	1.21 (0.14)	1.08 (0.12)	1.25 (0.15)	1.19 (0.14)	1.31 (0.12)
AD-positive (count value $\leq$1.21) FDG-PET (%)	19.9	24.3	53.7	90.8	40.0	58.1	19.9
Hippocampal volume (mm^3)	3669 (427)	3629 (516)	3239 (559)	2868 (489)	3431 (576)	3249 (531)	3633 (556)
AD-positive ($\leq$3260 mm^3) hippocampal volume (%)	16.0	23.3	52.4	77.6	36.6	50.0	21.7
CSF p-tau_{181} (pg/mL)	22.5 (11.3)	22.6 (11.2)	33.3 (16.5)	40.4 (20.3)	27.9 (15.8)	35.8 (17.1)	19.1 (7.4)
AD-positive (>23 pg/mL) CSF p-tau_{181} (%)	33.3	38.1	68.9	81.6	51.1	77.9	21.3

Abbreviations: HS, healthy elderly subjects; eMCI, early mild cognitive impairment; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; CSF, cerebrospinal fluid; FDG-PET, [18F] fluorodeoxyglucose positron emission tomography; p-tau_{181}, tau phosphorylated at threonine 181.

NOTE. Data are presented as mean (SD) or relative (in %) frequencies. Aβ (+) indicates participants with β-amyloid 1-42 levels in CSF lower $\leq$192 pg/mL. Aβ (−) indicates participants with β-amyloid 1-42 concentrations in cerebrospinal fluid >192 pg/mL.