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.

3. Results

The demographic characteristics, Mini-Mental State Examination scores, *APOE* ε4 status, biomarker data of the study sample, and number of AD-positive findings are presented in Table 1. The proportion of cases in each diagnostic group with one, two, or three positive biomarkers is presented in Fig. 1. Cohen κ values and percent agreement between the biomarkers are summarized in Table 2. Only poor agreements were detected, with the highest $\kappa = 0.34$ for MET/HIP (68.9% agreement) in the whole sample. In a post hoc analysis, excluding participants with biomarker values within ±1/4 standard deviation from the cutoff resulted in some improvement in agreement degree: κ for MET/HIP, MET/p-tau, and HIP/p-tau rose to 0.45, 0.42, and 0.33, respectively (whole sample).

Neither diagnosis nor *APOE* ε4 status influenced the distribution of agreement between the biomarkers (P's $\geq .111$ and .120, respectively). In the whole sample, κ's were higher in amyloid-positive than in amyloid-negative participants (Table 2). This difference reached the significance level for HIP/p-tau ($P = .002$), whereas there was a trend for MET/p-tau and MET/HIP ($P = .06$ and .085, respectively). Still, poor agreement degree was found among amyloid-positive participants (Table 3).

4. Discussion

As the authors of the new NIA-AA diagnostic guidelines note, the likelihood of conflicting biomarker data represents a limitation of the proposed algorithm [1,2]. The present study explicitly addresses this issue by estimating the agreement/disagreement between the major biomarkers of neuronal injury in the multicenter setting of the ADNI. Quite unexpectedly, we found a poor degree of agreement, with conflicting biomarker data in roughly every third subject. Thus, according to the proposed guidelines, 37% of MCI subjects should be assigned to the category "uninformative," that is, such biomarker findings cannot be taken into account in the diagnostic algorithm. Notably, the same degree of diagnostic certainty is assigned to cases in which no biomarker data are available. These results strongly suggest a need for differential consideration of the biomarkers of neuronal injury within the proposed diagnostic algorithm.

In fact, the different biomarkers of neuronal injury track distinct aspects of the AD pathophysiological process. That is, AD-related glucose hypometabolism is regarded to reflect reduction in synaptic density/activity and phenomena of diaschisis, hippocampal atrophy—neural loss, while elevated CSF p-tau—intracellular hyperphosphorylation of tau [3]. The limited agreement found can further be explained by the dynamic character of biomarker changes, such that the different biomarkers of neuronal injury become abnormal at different time points of the disease course [3,20]. Yet, the low degree of agreement even among patients with dementia suggests additional factors to play a role. Among them is, for example, clinical misdiagnosis. That is, roughly 10% of patients with probable AD had normal CSF $A\beta_{1\text{-}42}$ levels. Notably, all of them were positive for at least one marker of neuronal injury (data not shown). In

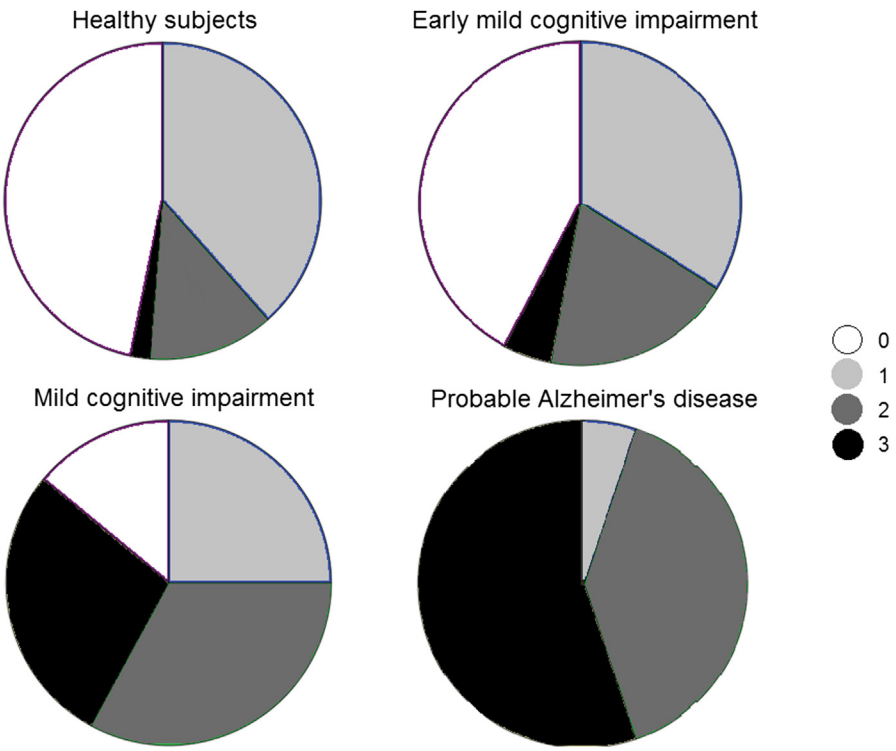

Fig. 1. Proportion of participants with one, two, three, or no positive biomarkers.

Table 2
Agreement between biomarkers of neuronal injury

	HS	eMCI	MCI	AD	All	Aβ (+)	Aβ (−)
N	156	189	164	76	585	308	277
MET/HIP	κ = 0.05	κ = 0.18	κ = 0.24	κ = 0.04	κ = 0.34	κ = 0.32	κ = 0.16
	P = .572	P = .012	P = .002	P = .679	P < .001	P ≤ .001	P = .010
	a = 71.8	a = 70.4	a = 62.2	a = 73.7	a = 68.9	a = 65.9	a = 72.2
p-tau/MET	κ = 0.12	κ = 0.13	κ = 0.24	κ = −0.14	κ = 0.29	κ = 0.15	κ = 0.01
	P = .119	P = .056	P = .002	P = .187	P < .001	P = .003	P = .916
	a = 64.7	a = 61.9	a = 62.8	a = 72.4	a = 64.3	a = 61.4	a = 67.5
p-tau/HIP	κ = −0.01	κ = 0.15	κ = 0.17	κ = −0.09	κ = 0.24	κ = 0.12	κ = 0.05
	P = .877	P = .027	P = .023	P = .422	P < .001	P = .013	P = .429
	a = 60.9	a = 63.0	a = 59.2	a = 64.5	a = 61.5	a = 55.8	a = 68.2

Abbreviations: HS, healthy elderly subjects; eMCI, early mild cognitive impairment; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; p-tau$_{181}$, tau phosphorylated at threonine 181; MET, regional metabolism on FDG-PET; HIP, hippocampal volume on MRI.

NOTE. Aβ (+) indicates participants with β-amyloid 1-42 levels in cerebrospinal fluid (CSF) lower ≤192 pg/mL; Aβ (−) indicates participants with β-amyloid 1-42 concentrations in cerebrospinal fluid >192 pg/mL.

a similar vein, the term "suspected non-AD pathophysiology (SNAP)" has been recently proposed to designate subjects without evidence of amyloid accumulation but with abnormal biomarkers of neuronal injury [4,21]. Such individuals present with a variable positivity for markers of neurodegeneration, likely as a sign of heterogeneous (non-AD) underlying pathology [4]. Here, the proportion of SNAP among HSs and patients with MCI was quite substantial (17%–32%, data not shown) and well comparable with that in the population-based studies [4,21]. This discussion is closely related to the critical issue of specificity of the currently acknowledged AD biomarkers. In particular, hippocampal atrophy was found, for example, also in patients with cerebrovascular, Parkinson disease, and semantic dementia. Yet, a nearly identical rate of positive biomarker findings (20%–21%) among amyloid-negative participants of the present study does not indicate disadvantageous specificity of any particular biomarker tested. Finally, the low degree of agreement in the present study can partly be related to methodological issues such as inaccuracies in image preprocessing/analysis, CSF peptide measurements, and suboptimal cutoff values. These potential confounds would primarily concern subjects with borderline or, according to the guidelines [1], "indeterminate" biomarker values, resulting in possibly incorrect categorization. Indeed, after exclusion of subjects with biomarker values close to the cut-off higher values of agreement were detected for all pairs of biomarkers. However, the (moderate) agreement reached is still not sufficient to justify uniform treatment of the given markers.

In the whole sample, higher κ values were found in amyloid-positive than in amyloid-negative participants. This observation in part supports the proposed model of AD development, in which amyloid deposition acts as a trigger of downstream neurodegenerative processes [3,20]. However, the percent agreement in the amyloid-positive group was still below 66%, and low κ values were found also among amyloid-positive participants. Thus, despite the common pathophysiological process in the form of amyloid deposition, the different aspects of AD-related neurodegeneration seem to vary to a substantial degree in individual subjects, even at the stage of dementia. That is, the agreement was not dependent

Table 3
Agreement between biomarkers of neuronal injury separately among Aβ (+) and Aβ (−) participants

	Aβ (+)				Aβ (-)			
	HS	eMCI	MCI	AD	HS	eMCI	MCI	AD
N	51	68	120	69	105	121	44	7
MET/HIP	κ = 0.15	κ = 0.15	κ = 0.20	κ = 0.04	κ = −0.03	κ = 0.18	κ = 0.02	κ = NA
	P = .275	P = .209	P = .028	P = .722	P = .741	P = .046	P = .913	P = NA
	a = 68.6	a = 63.2	a = 62.5	a = 72.5	a = 73.3	a = 74.4	a = 61.4	a = NA
p-tau/MET	κ = 0.23	κ = 0.11	κ = −0.04	κ = −0.13	κ = −0.09	κ = 0.01	κ = 0.13	κ = NA
	P = .047	P = .243	P = .655	P = .280	P = .367	P = .887	P = .395	P = NA
	a = 58.8	a = 50.0	a = 60.0	a = 76.8	a = 67.6	a = 68.6	a = 70.5	a = NA
p-tau/HIP	κ = −0.02	κ = 0.16	κ = −0.03	κ = −0.01	κ = −0.02	κ = 0.05	κ = 0.21	κ = −0.31
	P = .826	P = .067	P = .669	P = .941	P = .814	P = .558	P = .16	P = .088
	a = 43.1	a = 51.5	a = 55.8	a = 69.6	a = 69.5	a = 69.4	a = 68.2	a = 14.3

Abbreviations: a, percent agreement; κ, kappa coefficient; HS, healthy elderly subjects; eMCI, early mild cognitive impairment; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; MET, regional metabolism on FDG-PET; HIP, hippocampal volume on MRI; p-tau$_{181}$, tau phosphorylated at threonine 181; NA, nonapplicable because MET is a constant.

NOTE. Aβ (+) indicates participants with β-amyloid 1-42 levels in cerebrospinal fluid lower ≤192 pg/mL. Aβ (−), participants with β-amyloid 1-42 concentrations in cerebrospinal fluid >192 pg/mL.

on severity of the clinical manifestation in the present data, as reflected by low values of agreement in all diagnostic categories. Prospective diagnostic criteria of AD should address the relative importance of biomarkers of neuronal injury and elaborate a way of dealing with conflicting biomarker findings.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer Drug Discovery Foundation; BioClinica, Inc; Biogen Idec; Bristol-Myers Squibb; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech; GE; Innogenetics, N.V.; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development, LLC; Medpace, Inc; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Novartis; Pfizer; Piramal Imaging; Servier; Synarc Inc; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles.

RESEARCH IN CONTEXT

1. Systematic review: We searched for studies that had assessed (a) relationship between different biomarkers of Alzheimer's disease (AD) and (b) clinical applicability of the new diagnostic guidelines of the National Institute on Aging and the Alzheimer's Association.
2. Interpretation: Our findings indicate only poor agreement between biomarkers of neuronal injury, irrespective of the diagnostic status. Consequently, the different biomarkers of neuronal injury cannot be treated equally in terms of diagnostic utility, as is proposed in the guidelines.
3. Future directions: Prospective diagnostic criteria of AD should address the relative importance of markers of neuronal injury and elaborate a way of dealing with conflicting biomarker findings.

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