Application of the National Institute on Aging–Alzheimer's Association AD criteria to ADNI

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ABSTRACT

Objective: We describe the operationalization of the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup diagnostic guidelines pertaining to Alzheimer disease (AD) dementia in a large multicenter group of subjects with AD dementia.

Methods: Subjects with AD dementia from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with at least 1 amyloid biomarker (n = 211) were included in this report. Biomarker data from CSF Aβ42, amyloid PET, fluorodeoxyglucose-PET, and MRI were examined. The biomarker results were assessed on a per-patient basis and the subject categorization as defined in the NIA-AA workgroup guidelines was determined.

Results: When using a requirement that subjects have a positive amyloid biomarker and single neuronal injury marker having an AD pattern, 87% (48% for both neuronal injury biomarkers) of the subjects could be categorized as "high probability" for AD. Amyloid status of the combined Pittsburgh compound B–PET and CSF results showed an amyloid-negative rate of 10% in the AD group. In the ADNI AD group, 5 of 92 subjects fit the category "dementia unlikely due to AD" when at least one neuronal injury marker was negative.

Conclusions: A large proportion of subjects with AD dementia in ADNI may be categorized more definitively as high-probability AD using the proposed biomarker scheme in the NIA-AA criteria. A minority of subjects may be excluded from the diagnosis of AD by using biomarkers in clinically categorized AD subjects. In a well-defined AD dementia population, significant biomarker inconsistency can be seen on a per-patient basis. *Neurology*® 2013;80:2130–2137

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CI** = confidence interval; **FDG** = fluorodeoxyglucose; **HVa** = hippocampal volume adjusted by total intracranial volume; **NIA-AA** = National Institute on Aging–Alzheimer's Association; **pAD** = probable Alzheimer disease; **PiB** = Pittsburgh compound B; **SNAP** = suspected non-Alzheimer pathway.

Recent recommendations from the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup for clinical diagnostic guidelines (NIA-AA-C) for Alzheimer disease (AD) dementia have integrated biomarkers into the diagnostic algorithm of AD.[1] The diagnostic category of probable AD (pAD) dementia is modified by the results of biomarker findings.

Many investigators have validated biomarkers using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Biomarkers have been used to characterize diagnostic groups within the ADNI population.[2,3] AD subject fluorodeoxyglucose (FDG) categorization accuracy in ADNI was 85%[4] and had a sensitivity and specificity of 83% and 78% using a quantitative image analysis program.[5] Similar reports on FDG,[6] MRI,[7] or CSF[8] performance are based on ADNI subject categorization. Investigators have evaluated the interaction of biomarker modalities in defining the ADNI subject groups.[2,9–11] Other publications predict which subjects will progress to AD using MRI.[12–16] Others have derived new analysis methods for imaging biomarker data[17–27] or developed theories of biomarker progression patterns.[28] To our knowledge, the NIA-AA-C criteria have not yet been studied in a systematic manner.

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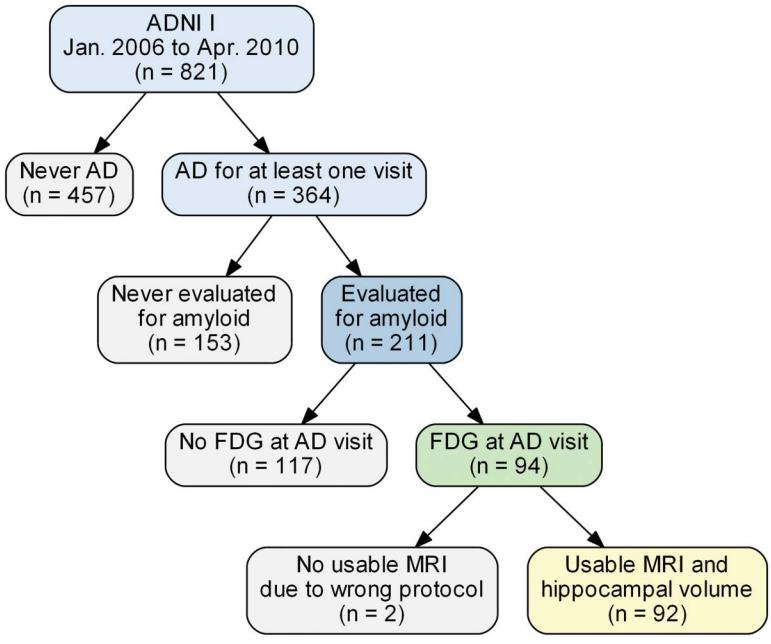
The ADNI AD dementia population also provides a group of pAD subjects with standardized biomarker assessments by which to operationalize the NIA-AA-C recommendations and give insight into the clinical patient-by-patient impact of the categorization. In this article, we describe an operationalization of the pAD diagnostic recommendations using amyloid and neuronal injury biomarkers and describe potential alterations in diagnostic categories of pAD of the ADNI subject group based on the new NIA-AA workgroup's recommendations.

METHODS

Dementia categorization by NIA-AA. The NIA-AA workgroup's new schema is published elsewhere.[1] Notably, some of the diagnostic categories within the pAD dementia group are altered by biomarkers in the schema to become 1) "high probability," 2) "diagnosis based solely on clinical findings," and 3) "dementia unlikely due to AD" with several associated biomarker probability categorizations.

Subjects. The ADNI is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. A detailed discussion of ADNI, the included subjects, and the forthcoming data being provided is found elsewhere.[29] In this report, we included subjects from ADNI-1 that had a diagnosis of AD dementia at any visit and either amyloid PET imaging or CSF β-amyloid (Aβ)42 as a measure of amyloid pathology. The clinical diagnosis of AD dementia in ADNI-1 was based on the 1984 pAD criteria[30]; however, the clinical criteria of 1984 and 2011 are very similar.[1] Subjects were recruited based on clinical diagnoses; although MRI was used to rule out other diagnoses, neither MRI nor PET imaging was likely to have been involved in the initial diagnosis. FDG and MRI were performed a median of 8 days apart (range, 3 months) and were performed at the time of the most recent AD dementia diagnosis of record. Of 364 eligible subjects with a diagnosis of AD dementia for at least one visit, 211 had an amyloid biomarker test and all of these had MRI as well. Of these 211, 94 underwent FDG-PET and MRI, which were used as neuronal injury biomarkers. Two of these 94 had unusable or incorrect MRI examinations and thus hippocampal volumes could not be estimated (figure 1). Of the 211, 200 MRIs could be analyzed for hippocampal volume estimates.

Figure 1 Flow chart of subject selection



Flow diagram showing the selection method of subjects for analysis from the ADNI-1 cohort. AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; FDG = fluorodeoxyglucose.

Standard protocol approvals, registrations, and patient consents. All participating ADNI sites obtained local institutional review board approval and informed subject consent for enrollment in the ADNI study.

PET, MRI, and CSF methods. ADNI has standardized biomarker acquisition and performance methods that are used in the trial and are described elsewhere.[31–33]

All C-11 Pittsburgh compound B (PiB) scans from the ADNI group were analyzed using our in-house automated analysis method,[34] and a cortical-to-cerebellar ratio of the global (prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions) PiB cortical-to-cerebellar ratio measurement of >1.5 was considered positive. So as not to overstate the precision of our estimates, we analyzed ratios to 2 significant digits.

All FDG-PET scans were analyzed using a quantitative statistical analysis program, Cortex ID (GE Healthcare, Inc., Milwaukee, WI), to produce FDG surface projections and *z*-score statistical maps. This method of analysis has become widespread in clinical practice and was therefore used to attempt to reflect the performance of FDG-PET in clinical practice. Such quantitative procedures result in an observer-independent quantitative mapping of regional glucose metabolic abnormalities that optimize FDG-PET interpretation on an individual patient level, as we have reported elsewhere.[35] Each subject's quantitative map was reviewed in a blinded manner by 2 expert reviewers (V.J.L., P.J.P.) who characterized the patterns of FDG abnormality as AD-like (predominant posterior cingulate, parietal, and posterior temporal hypometabolic patterns), frontotemporal dementia–like (predominant frontal and anterior temporal hypometabolism), or other (normal, undetermined, or Lewy body dementia pattern). Thereafter, for purposes of NIA-AA-C category assignment, these classifications were collapsed to AD-like or non-AD. In the case of disagreement, a consensus diagnosis was reached and used as the final diagnosis.

MRI analysis was performed using FreeSurfer 4.5, an analysis tool frequently used in research settings, to determine hippocampal volume. Based on a disease cutoff on prior autopsy-correlated MRI analysis,[36] and using an adjustment for total intracranial volume, an adjusted volume (HVa) cutoff of -0.48 cm^3 was used to determine abnormality. With this cutoff, subjects with hippocampal volumes more than approximately 0.5 cm^3 below what is expected given their total intracranial volume were considered abnormal.

CSF analysis was performed at the ADNI core laboratory and the values from "File 2" covering baseline and 12-month follow-up CSF samples were used. The data were evaluated based on a CSF Aβ42 cutoff level of $\leq$192 pg/mL considered abnormal. Detailed description of the collection and analysis of CSF in the ADNI Biomarker Core is described elsewhere.[33]

Statistical methods. We summarized distributions with medians and interquartile ranges or percentages and calculated confidence intervals for percentages using the Wilson method. The κ statistic was used as a measure of agreement between classes of biomarkers.

RESULTS

Amyloid biomarkers. Demographics between amyloid-positive and amyloid-negative subjects showed

significant differences for age, Mini-Mental State Examination scores, and *APOE* status (table 1). Two subjects were diagnosed with mild cognitive impairment after the initial diagnosis of pAD (one was amyloid positive, one was negative) and both were included. Forty of 46 subjects (87%) with clinically defined pAD had positive C-11 PiB-PET scans. In 42 cases of serial PiB scans, the most recent scan was used for further evaluation. Three subjects had a negative scan followed by a positive scan, and no subjects who had earlier positive scans had negative scans.

Seventeen of 192 subjects (9%, 95% confidence interval [CI] 5%–14%) had normal CSF Aβ42. The most recent measurement was used in 154 cases of serial CSF Aβ42. One subject had normal CSF at baseline and abnormal CSF by month 12, and all other subjects showed serial results that were diagnostically unchanged. The amyloid status of the combined PiB-PET and CSF results showed an amyloid-negative rate of 9.5% (20/211 subjects; 95% CI 6%–14%); 1 of 24 subjects had a positive PiB and negative CSF result in both tests ($\kappa = 0.78$). Therefore, 191 of 211 (90.5%) of the pAD group had at least one positive amyloid biomarker.

Neuronal injury biomarkers. FDG-PET showed an AD pattern in 63 of 94 subjects (67%). Therefore, 31 of 94 (33%, 95% CI 24%–44%) had a non-AD pattern. Seventy of 92 subjects (76%) had an abnormal HVa and 22 of 92 had a normal HVa (24%, 95% CI 16%–34%). Only 46 of 92 subjects (50%, 95% CI 40%–60%) had both abnormal HVa and an AD-like pattern on FDG-PET (table 2).

Agreement between amyloid and neuronal injury biomarkers. The NIA-AA criteria did not specify categories for all possible combinations of biomarkers. Some of the more common expected combinations are interesting to consider. When an AD pattern on FDG was seen, 95% (60/63) of the time the subjects were amyloid positive. However, in 26 of 86 subjects (30%) who were amyloid positive, non-AD FDG patterns were seen (table 3).

When abnormal HVa was seen, 93% (65/70) of the time the subjects were amyloid positive. However, in 20 of 85 subjects (24%) who were amyloid positive, abnormal HVa was not seen. FDG and MRI both showed typical AD findings in 44 of 85 subjects (52%) who were AD amyloid positive. Possible conflicting patterns of FDG and MRI findings were seen in 40 of 92 subjects with AD (43%) (table 3).

Many subjects did not have PET imaging and only had MRI available as a neuronal injury biomarker. A total of 200 subjects with amyloid biomarkers were available for MRI-only evaluation. Of the 200 subjects with AD dementia who had evaluable MRIs for hippocampal volume measurement, 159 of 200 (80%, 95% CI 73%–85%) had abnormal HVa and 41 of 200 (20%, 95% CI 15%–27%) had normal HVa.

NIA-AA categorization of ADNI subjects with AD dementia. At an individual subject level, there was substantial inconsistency in the biomarker findings in the ADNI

Table 1 Subject demographics: Amyloid-positive vs -negative subjects

		Amyloid positive		Amyloid negative	
	All (n = 211)	All (n = 191)	FDG and MRI negative (n = 5)	All (n = 20)	FDG and MRI negative (n = 1)
Female, n (%)	87 (41)	80 (42)	0 (0)	7 (35)	1 (100)
Age, y					
Median (IQR)	77 (71-82)	77 (71-81)	80 (80-85)	81 (75-85)[a]	72
Range	55-90	55-90	68-88	64-90	—
Education, y					
Median (IQR)	16 (13-18)	16 (13-18)	16 (12-18)	16 (12-16)	12
Range	4-20	4-20	10-20	8-20	—
CDR-SB score					
Median (IQR)	4.5 (3.5-6.0)	4.5 (3.5-6.0)	3.0 (3.0-4.0)	4.5 (2.9-5.5)	
Range	1-15	1-15	1.5-4.5	1-6	—
MMSE score					
Median (IQR)	23 (20-25)	23 (20-25)	26 (23-26)	25 (23-26)[b]	20
Range	5-30	5-30	20-27	20-29	—
APOE ε4, n (%)	140 (66)	137 (72)	2 (40)	3 (15)[c]	1

Abbreviations: CDR-SB = Clinical Dementia Rating–Sum of Boxes; FDG = fluorodeoxyglucose; IQR = interquartile range; MMSE = Mini-Mental State Examination.
[a] $p = 0.01$; [b] $p = 0.002$; [c] $p < 0.001$ vs all amyloid-positive subjects.

Table 2 Agreement among amyloid biomarkers, MRI, and FDG-PET[a]

	Aβ−[b]	Aβ+[b]	Percent Aβ+[b] (95% CI)
No. of subjects with amyloid testing			
C-11 PiB	6	40	87 (73-95)
CSF Aβ42	17	175	91 (86-95)
Combined (n = 211; 10% negative)	20	191	91 (86-95)
FDG clinical interpretation	8 (9% in Aβ− group with FDG)	86 (91% in Aβ+ group with FDG)	
AD-like	3 (38)	60 (70)	95 (86-99)
FTD-like	1 (12)	1 (1)	50 (9-91)
Indeterminate/other	4 (50)	25 (29)	86 (67-95)
Hippocampal status	7 (8% in Aβ− group with FDG and MRI)	85 (92% in Aβ+ group with FDG and MRI)	
Abnormal	5 (71)	65 (76)	93 (83-97)
Normal	2 (29)	20 (24)	91 (69-98)
Neuronal injury based on FDG and MRI	7 (8% in Aβ− group with FDG and MRI)	85 (92% in Aβ+ group with FDG and MRI)	
Both AD positive	2 (29)	44 (52)	96 (84-99)
MRI AD positive only	3 (43)	21 (25)	88 (67-97)
FDG AD positive only	1 (14)	15 (18)	94 (68-100)
Neither	1 (14)	5 (6)	83 (36-99)

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CI = confidence interval; FDG = fluorodeoxyglucose; FTD = frontotemporal dementia; PiB = Pittsburgh compound B.
[a] Data are n, n (%), or percent (95% CI).
[b] Aβ- and Aβ+ refer to total C-11 PiB and CSF Aβ42 categorical classifications.

pAD group. Only 48% showed a consistent amyloid and neuronal injury biomarker pattern across all biomarkers for pAD that could be categorized as high probability by the NIA-AA proposed criteria, using a requirement that all amyloid and neuronal injury markers show an AD pattern. When using a requirement that subjects have a positive amyloid biomarker and at least a single neuronal injury marker having an AD pattern, 87% of the subjects could be categorized as intermediate probability for AD. The latter requirement would ignore the negative findings of the other neuronal injury biomarker. Figure 2A shows the categorization of these findings by the NIA-AA published criteria. Notably, some subjects with positive amyloid biomarkers and negative neuronal injury biomarkers are left undefined by the NIA-AA-C AD dementia criteria. Based on our findings, we made minor modifications to the biomarker probability of AD assignments to account for this undefined group. It is important to note that negative amyloid status may actually be reasonably prioritized higher than that of the neuronal injury biomarkers, especially given these data that show significant variability in neuronal injury biomarkers, and represents a needed modification in order to optimally operationalize the application of biomarkers (figure 2B). In this assignment method, subjects with a single positive neuronal injury biomarker who are amyloid positive receive at least high-probability AD assignments. In addition, all subjects with negative amyloid biomarkers receive no higher than low-probability assignments.

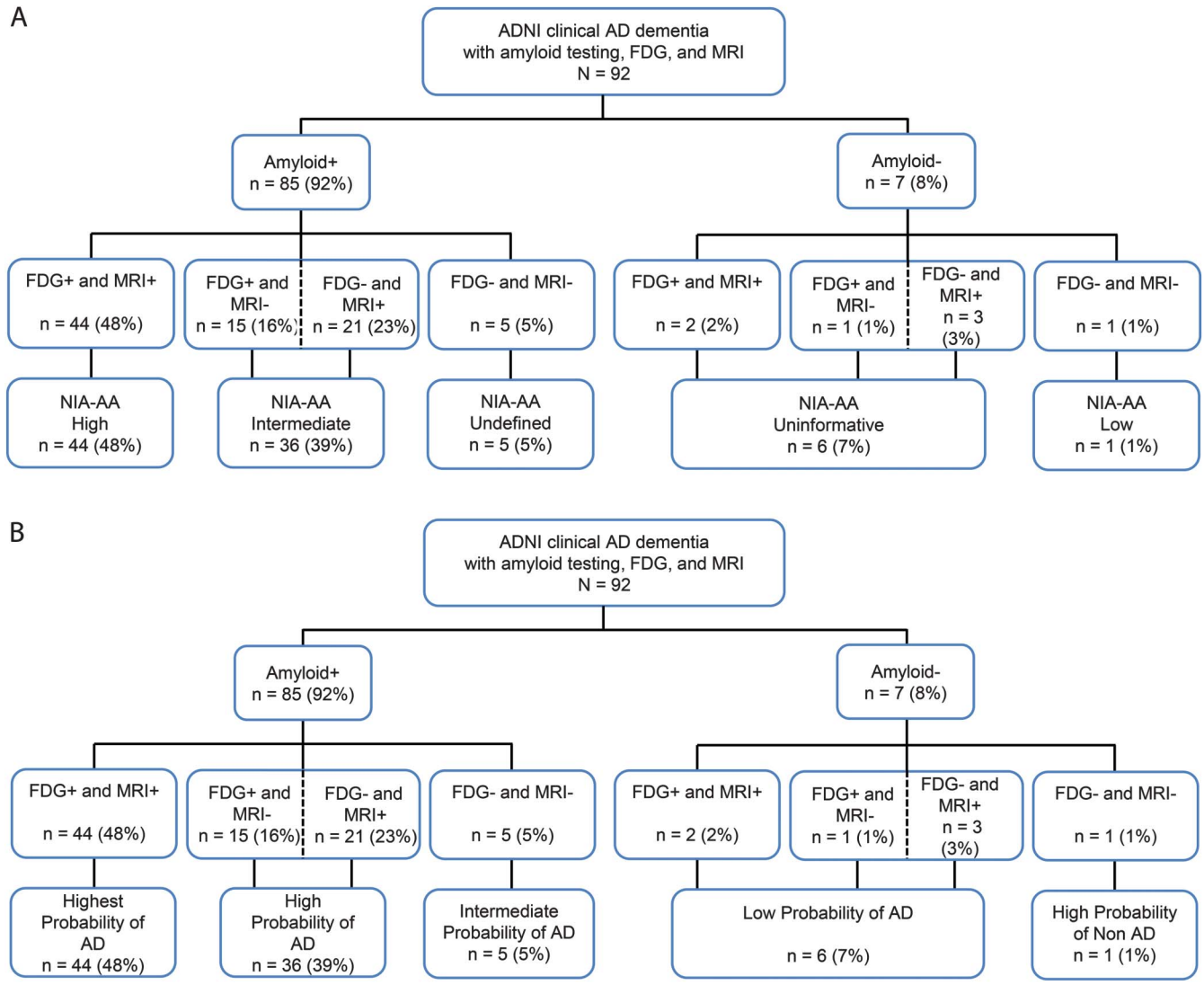
Table 3 Three-way agreement between biomarkers

Amyloid	FDG	MRI	Count, n (% in total Aβ sample)
Aβ+	AD	Abnormal	44 (48)
	AD	Normal	15 (16)
	FTD	Abnormal	1 (1)
	Other	Abnormal	20 (22)
	Other	Normal	5 (5)
Aβ−	AD	Abnormal	2 (2)
	AD	Normal	1 (1)
	FTD	Abnormal	1 (1)
	Other	Abnormal	2 (2)
	Other	Normal	1 (1)

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; FDG = fluorodeoxyglucose; FTD = frontotemporal dementia.

DISCUSSION The NIA-AA-C recommendations give several variations to a single diagnostic category of pAD. This report operationalizes these recommendations in a well-described, multicenter, clinically diagnosed AD

Figure 2 Flow charts of subject disease probability assignment



Flow charts showing the categorization of ADNI subjects with AD using the strict NIA-AA-C criteria (A) and Mayo-modified NIA-AA-C criteria (B). AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; FDG = fluorodeoxyglucose; NIA-AA-C = National Institute on Aging–Alzheimer's Association clinical diagnostic guidelines.

population. These findings have important implications relative to how the new NIA-AA criteria may function in clinical practice and also provide important insight into the ADNI AD subject group pertaining to diagnostic certainty of this AD group, at least as can be defined by the NIA-AA recommendations. Differences between a typical population sample and the ADNI group will nonetheless hamper a direct comparison of these data to a typical clinical sample because the ADNI subjects were largely recruited from AD research centers and as such represent a population with typical specialty care and research center enrollment biases. These findings may also aid researchers using the ADNI AD dementia group with a better understanding of these clinically diagnosed patients and the implications the makeup of the group may have in biomarker testing.

A substantial percentage (92%) of the ADNI AD dementia group had positive amyloid biomarkers (8% had negative amyloid biomarkers). Given the premise of the amyloid hypothesis of the pathogenesis of AD, and that amyloid biomarkers are more specific for AD than the neuronal injury biomarkers, this negative amyloid biomarker group could be considered to most likely not have AD if autopsy were performed and therefore represent other types of dementia. Of course, the rare possibility exists that AD autopsy-positive cases with negative amyloid biomarkers during life are undisclosed in these data, but such cases would only be clarified by autopsy data that are yet to be described in this group. The NIA-AA-C criteria require a diagnosis of "dementia unlikely due to AD" to also include negative neuronal injury makers. In this work, we show that 5 of 92 subjects (5%) fit this categorization, when at least one neuronal

injury marker is negative. If both neuronal injury markers were required to be negative, one subject would meet the "dementia unlikely due to AD" criteria. Notably, a larger number of subjects in the ADNI AD group had amyloid testing without FDG-PET and remain uncategorized by that single biomarker in the NIA-AA-C criteria.

Our analysis highlighted some areas in the NIA-AA-C criteria where further clarifications are needed. First, some direction may be needed to best approach the situation whereby amyloid imaging and CSF AB42 assays conflict, although this was seen in only one case and therefore at present lacks sufficient data to evaluate. Second, having several neuronal injury biomarkers to choose from has created difficulty in evaluating the relatively frequent situations whereby the neuronal injury biomarkers are conflicted. The NIA-AA workgroup did not have data on hand to deal with such conflicts. One could consider that if at least one neuronal injury biomarker is positive, that should be sufficient for meeting the criteria of a positive neuronal injury biomarker. Third, the NIA-AA-C criteria did not address the situation in which amyloid markers and neuronal injury biomarkers are in conflict. These cases may be in the high probability category if amyloid positive and low probability if negative, if the amyloid biomarker is allowed to take priority. The specific situation in which amyloid is normal and neuronal injury biomarkers are positive or conflict with one another could be considered low probability rather than uninformative as currently assigned by NIA-AA-C (figure 2).

We have previously reported a group of patients with normal amyloid biomarkers and abnormal neuronal biomarkers (FDG-PET or MRI) as a "suspected non-Alzheimer pathway" (SNAP) group.[37] This group exists in the Mayo Clinic Study of Aging normal and mild cognitive impairment populations at 23%[37] and 29%[38] rates, respectively. We presume that they represent some other pathology such as cerebrovascular disease or other neurodegenerative disease. This same SNAP characterization, while not clearly defined by the NIA-AA-C criteria as mentioned above, exists in the ADNI AD group at a 6% incidence. They represent a possible confounding variable to scientific evaluation of the ADNI AD data and are yet to be entirely understood clinically.

The imperfect correlation of clinical diagnoses and biomarker findings is expected but needs to be documented and considered as applied to clinical dementia practice and scientific evaluation. The clinical diagnosis of pAD is imperfect and in the primary care setting can have very low sensitivity ranging from 26% to 69%.[39] The accuracy of clinical diagnosis of pAD in medical specialty settings has been well described in comparison to autopsy data and has a higher sensitivity in the range of 75%.[40] The clinical diagnosis can be hampered because biomarkers have less than perfect accuracy on an individual basis. Although the biomarkers have been shown to stratify the disease populations within ADNI at statistically significant levels, their application to individual patients may be less clear. With this in mind, it is helpful to understand that in clinical practice, and extrapolating from what is seen in the ADNI AD dementia population, one may not expect to see more than an approximately 50% concordance rate of all biomarkers with a clinical diagnosis of pAD. It also was not obvious that any biomarker was clearly superior in this group of subjects; however, disease validation was limited, the data were limited by a very low number of amyloid-negative subjects by which to test biomarker specificity, and we lack a means of validating the underlying pathology in these participants.

Although this falls short of any expectation that biomarkers will increase the diagnostic confidence for every patient with AD and give a "high" NIA-AA-C probability of AD, it is helpful to know that about 10% of subjects could be ruled out for pAD. To this point, the utility of amyloid imaging in clinical practice is moving in the direction of using amyloid biomarkers as a "rule out of AD," with the recent US Food and Drug Administration approval of Florbetapir described as being inconsistent with a neuropathologic diagnosis of AD if the amyloid scan is negative.

An additional point relevant to our methods is that we used hippocampal volume as our MRI measure of neuronal injury. The nonspecificity of hippocampal volume loss (present in frontotemporal lobar degeneration, hippocampal-sparing AD, cerebrovascular disease, or hippocampal sclerosis) needs to be considered in that it could occur with other diseases and thereby reduce the accuracy of this biomarker in subjects with pAD. In this set of subjects with pAD, we opted for this method because of our ability to characterize the finding on an individual patient basis and because optimizing sensitivity for disease was one of our primary concerns in this early test of biomarker positivity in the pAD group. It could be considered one of several ways of categorizing MRI findings in this group, only one of which we evaluated in this work.

In contrast, the FDG-PET disease categories were based on pattern recognition by trained nuclear medicine physicians aided by quantitative analysis. This method allowed for more detailed category parsing of the imaging data that was not done for MRI. Similar pattern recognition evaluation of MRI data in the future may be a useful exercise.

In the ADNI pAD population, about 5% of the population fits the NIA-AA-C criteria of "dementia unlikely due to AD." In addition, about 10% of the ADNI subjects with pAD are amyloid biomarker negative, suggesting that they may not have Alzheimer-type pathology as a cause of their dementia. More correlation and validation studies of biomarkers in the AD population will be essential to understand biomarker performance and correlation with autopsy data.

AUTHOR CONTRIBUTIONS

Dr. Lowe designed the study, took part in data collection, performed and supervised all analyses, generated the first and final drafts, and takes overall responsibility for the data and the manuscript. Dr. Peller took part in image analyses and critically reviewed the manuscript. Mr. Weigand performed data analyses and critically reviewed the manuscript. Ms. Montoya Quintero performed image analyses. Ms. Tosakulwong performed data analyses. Dr. Vemuri and Mr. Senjem performed analyses of imaging data and critically reviewed the manuscript. Mr. Jordan performed image analyses and critically reviewed the manuscript. Dr. Jack, Dr. Knopman, and Dr. Petersen took part in data collection and critically reviewed the manuscript.

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