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Value of Diagnostic Tests to Predict Conversion to Alzheimer's Disease in Young and Old Patients with Amnestic Mild Cognitive Impairment

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Abstract. Using the database of the Alzheimer's Disease Neuroimaging Initiative, we examined the value of neuropsychological assessment, structural magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) biomarkers, and FDG-PET scanning with respect to prediction of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD). We tested the hypothesis that CSF biomarkers and FDG-PET would lose prognostic value when applied in patients older than 75 years, whereas MRI and neuropsychological testing would not. At baseline 175 patients had MCI, mostly amnestic. They were followed during a mean of 2.7 years, and 81 patients converted to AD after a mean of 1.6 years. Logistic regression analyses showed that neuropsychological assessment and MRI variables predicted conversion with 63 to 67% classification success both in patients younger and older than 75 years, while CSF biomarkers attained this success rate only in patients younger than 75 years. For FDG-PET, this rate was 57% in the total sample. We conclude that the diagnostic yield of different techniques in predicting conversion from MCI to AD is moderate, and that it is affected by age of the subject under study. MRI and neuropsychological assessment remain informative in patients older than 75 years, unlike CSF biomarkers.

Keywords: Alzheimer's disease, amyloid, cerebrospinal fluid, FDG-PET, mild cognitive impairment, MRI, neuropsychological tests, tau protein

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INTRODUCTION

For subjects with memory complaints and for their relatives as well, it is paramount that physicians can reliably distinguish between normal aging and mild cognitive impairment (MCI) or early Alzheimer's disease (AD). Also, in research on the early stages of (incipient) dementia it is highly relevant to differentiate between these conditions, e.g., for selection of subjects for early therapeutic interventions, if these would become available in the future.

[1]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). 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. ADNI investigators include (complete listing available at http://adni.loni.ucla.edu/research/active-investigators/).

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Diagnostic techniques vary with respect to their capacity to do so. Studies examining a single technique such as cerebrospinal fluid (CSF) biomarkers, neuroimaging, or neuropsychological testing often show high diagnostic accuracies [1–3]. Comparisons of these diagnostic techniques in the same patient sample, however, show a more variable picture. For example, one such comparison found that memory performance, hippocampal volume, and brain glucose metabolism as assessed by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning distinguished AD patients better from control subjects than CSF biomarkers, while a combination of memory performance and FDG-PET best predicted conversion from MCI to AD [4]. Another study found that memory performance and odor identification were slightly stronger predictors of conversion to AD than medial temporal lobe volume as assessed by magnetic resonance imaging (MRI) [5]. Furthermore, clinical characteristics, especially everyday functioning, and memory and executive performance, seem to predict conversion to AD better than other markers, including CSF biomarkers, APOE genotype, and most brain volumetric measures [6]. These direct comparisons are in line with the indirect comparative results of a meta-analysis that we conducted of earlier studies [7].

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we recently showed that the differences between techniques with respect to diagnostic potential are especially pronounced in relatively old subjects [8]. CSF biomarkers and FDG-PET scanning lose potential for diagnosing AD when used in subjects of 75 years of age or older compared to younger age cohorts, whereas the diagnostic value of structural MRI and neuropsychological assessment is not affected by the age of the subject under study [8, 9]. This vulnerability of diagnostic methods to age effects is important, because 1) most AD patients are older than 75 years [10]; 2) the association between clinical dementia and neuropathological characteristics of AD is weaker at higher ages [11]; and 3) other brain diseases mimicking a clinical AD syndrome become more prevalent with increasing age [12].

In the present study, we investigated how well these techniques perform at different ages in predicting disease progression from MCI to AD. Based on our previous findings [8], we expected all four diagnostic techniques to contribute in predicting conversion to AD in relatively young MCI patients, but that only neuropsychological assessment and MRI would predict conversion in relatively old patients.

MATERIALS AND METHODS

Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. In principle, all subjects are re-examined at six-month intervals. For up-to-date information see http://www.adni-info.org.

Subjects

From the ADNI database (accessed June 18, 2011), we included all MCI subjects ($n = 175$; 44% of the 398 MCI patients in ADNI) who had a lumbar puncture to obtain CSF. All patients had undergone neuropsychological testing and MRI scanning, and 89 also had a FDG-PET scan. Subjects were included if they were in good physical and mental health. MCI was defined by the Petersen criteria [13], i.e., memory complaints corroborated by an abnormal score on the delayed paragraph recall subtest of the Wechsler Memory Scale-Revised, a normal Mini-Mental Status Examination (MMSE) score (> 23), a Clinical Dementia Rating (CDR) score of 0.5, and not satisfying consensus criteria for dementia. Conversion to AD on follow-up was defined by NINCDS/ADRDA criteria of probable AD, including a MMSE score between 20 and 26, and a

CDR score of at least 0.5. Subjects who used drugs with anti-cholinergic or narcotic properties were excluded, but use of estrogens, cholinesterase inhibitors, or vitamin E was allowed if the dose remained stable. For details on in- and exclusion criteria see Petersen et al. [13] or http://www.adni-info.org.

Neuropsychological evaluation

To avoid circular reasoning, we analyzed only baseline neuropsychological test results that were not used for defining the groups or for establishing a diagnosis during follow-up (i.e., WMS-R paragraph recall, MMSE). This left the following tests: Alzheimer's Disease Assessment Scale cognitive section (ADAS-cog; total score and the items immediate and delayed word recall), Rey's Auditory Verbal Learning Test (RAVLT; total number of words reproduced in five learning trials; number of words reproduced after a delay of about 30 min), category fluency (number of animals and vegetables named in 1 min each), Boston Naming Test, Trail Making Test parts A and B, Letter Digit Substitution Test (LDST), Digit Span forward and backward from the Wechsler Adult Intelligence Scale, and the Clock Drawing task (free drawing and copying). For references see [13–15].

CSF

CSF biomarker variables included amyloid-β ($A\beta)_{1\text{-}42}$, total-tau, and phospho-tau, phosphorylated at threonine 181, in pg/mL ($p\text{-}tau_{181p}$), as well as ratios ($t\text{-}tau/A\beta_{1\text{-}42}$, $p\text{-}tau_{181p}/A\beta_{1\text{-}42}$). Methods for analysis have been previously described [16, 17] and are provided at http://www.loni.ucla.edu/ADNI.

MRI

Structural magnetic resonance scans (1.5-T) were acquired at multiple ADNI sites using a standardized MRI protocol described elsewhere. [18] Total brain volume, ventricular volume, and volumes of left and right hippocampi, fusiform gyri, middle and inferior temporal lobes, entorhinal cortices, and inferior lateral ventricles were obtained using voxel based morphometry. Since an earlier study did not find significant differences between left and right structures in the ADNI data, [19] we used the mean of left and right volumes of each structure.

FDG-PET

Using FDG-PET acquired, controlled, and analyzed according to the ADNI protocol, region of interest (ROI) approaches (UC Berkeley) resulted in a set of five regions located in right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. Because these ROIs were highly correlated [20], we averaged them across subjects. This composite ROI was used in the present analyses.

Statistical analyses

All variables were corrected for age, gender, and education based on the regression weights in the normal control group of the ADNI project as described elsewhere [8]. Next, we reduced the number of variables by examining which variables of each technique best predicted conversion to AD. This was done by separate logistic regressions for each of the techniques with conversion (yes/no) as the dependent variable. The variables of each technique were entered in a stepwise forward manner. We then repeated this analysis combining all significant (at $p < 0.10$) predictors of the separate logistic regressions; these were again entered in a stepwise forward fashion.

The predicted probabilities of conversion to AD were calculated for each patient in each of the logistic regression models. If this predicted probability for a subject was <0.5, the prediction was that he would not convert; if it was >0.5 conversion was predicted. These predictions were compared to the subjects' actual status (conversion or no conversion), which gave an estimate of the a posteriori classification success rate. Next, the receiver operating characteristics (ROC) of these predicted probabilities were analyzed to calculate the area under the curve (AUC). This was done to enable a direct comparison of the three techniques and their combinations. p-values ≤ 0.05 were considered significant unless stated otherwise. All analyses were done with SPSS 18.0.

To examine the effect of age on the predictive value of the techniques, the sample was split at the median age, and the same analyses were repeated in both halves.

RESULTS

Patient characteristics at baseline are shown in Table 1. These characteristics were not different from those of the total MCI sample [13]. The same was true for the 89 subjects who had undergone FDG-PET

Table 1
Baseline characteristics of the patients; percent or mean (standard deviation)

	Stable ($n=94$)	Converted ($n=81$)	p
Percent female	32%	38%	0.43
Age	74.1 (7.6)	74.4 (7.4)	0.77
Education years	15.8 (3.0)	15.6 (3.0)	0.44
MMSE score	27.2 (1.7)	26.6 (1.8)	0.02

scanning. Follow-up duration varied between 0.5 and 4.6 years (mean 2.7, SD 0.9). During the course of the study, 81 patients (46%) converted from MCI to AD after a mean of 1.6 (SD 0.8) years. The conversion rate was similar (43%) in the subgroup with PET scan, and in the total MCI sample (42%). Time to conversion was also comparable in these subsamples.

The results of the logistic regression and ROC analyses of the entire sample are shown in Table 2 (column 'all subjects'). For each technique separately, and for combinations of techniques, the table lists percentages of variance explained by the regression models, percentages of correct predictions, the AUCs, and the significant predictors. Under the assumption that all patients remained stable, the *a priori* classification rate would be 54% correct, because 94 out of the 175 MCI patients remained stable. The *a priori* success rate would be 46% (i.e., 81/175) in this sample under the assumption that all patients would convert to AD. This is equivalent to the base rate or the pre-test probability of disease. Additional diagnostic assessments are useful to the degree in which they are able to raise this classification success rate. The a posteriori classification success varied from 57% correct for FDG-PET results to 66% for MRI, with CSF and neuropsychological assessment in between. For each diagnostic technique, one or two variables with significant predictive value were selected by the analyses; the remaining variables did not significantly contribute to the models. The analysis of the combination of neuropsychological tests, CSF biomarkers, and MRI selected one variable

Table 2
Results of logistic regression and receiver operating characteristics analyses comparing diagnostic techniques in relatively young ($n=87$) and relatively old age cohorts ($n=88$) with respect to the prediction of conversion from MCI to AD

	Young (<75 yrs)	Old (>74 yrs)	All subjects
Neuropsychology			
% explained variance	23	10	18
% correct	67	64	64
AUC (90% CI)	0.73 (0.64–0.82)	0.65 (0.55–0.74)	0.70 (0.63–0.76)
Significant predictors	AVLT total	ADAS-cog DR	ADAS-cog DR AVLT total
CSF			
% explained variance	20	5*	11
% correct	64	60	63
AUC (90% CI)	0.70 (0.61–0.79)	0.59 (0.49–0.69)	0.65 (0.58–0.71)
Significant predictors	amyloid-β	amyloid-β	amyloid-β
MRI			
% explained variance	22	16	18
% correct	65	63	66
AUC (90% CI)	0.73 (0.64–0.82)	0.70 (0.62–0.79)	0.71 (0.64–0.77)
Significant predictors	hippocampi	inferior-temporal	hippocampi medio-temporal
FDG-PET			
% explained variance	9*	ns	7
% correct	55	ns	57
AUC (90% CI)	0.65 (0.52–0.79)	ns	0.61 (0.51–0.71)
Combined, no PET			
% explained variance	38	22	27
% correct	72	71	70
AUC (90% CI)	0.79 (0.71–0.87)	0.74 (0.65–0.82)	0.76 (0.70–0.81)
Significant predictors	AVLT total hippocampi amyloid-β	inferior-temporal ADAS-cog DR	AVLT total hippocampi amyloid-β
Combined, with PET			
% explained variance	48	ns	19
% correct	82	ns	65
AUC (90% CI)	0.75 (0.67–0.84)	ns	0.68 (0.62–0.75)
Significant predictors	AVLT total amyloid-β	ns	AVLT total

Note: ns = not significant ($p>0.10$) * = borderline significant ($0.05<p<0.10$); % explained variance = Nagelkerke's R-square; % correct = % correct classifications (a priori success rate = 54%); AVLT = Rey's Auditory Verbal Learning Test; total = total learning score, DR = delayed recall.

with predictive value from each technique. The combination predicted conversion to AD slightly better than each technique separately, although the differences between the resulting predictive models were not statistically significant, as can be deduced from the overlap of the AUC confidence intervals (Table 2). When FDG-PET was added to this combination, it was not entered into the model ($p = 0.11$); only memory performance was significant in this model.

Effect of age

The sample was split at the median into <75 years (young; $n = 87$, 40 converters) and >74 (old; $n = 88$, 41 converters). The same logistic regression and ROC analyses were repeated for each of the four techniques and for the techniques combined. The middle two columns of Table 2 summarize the results. Neuropsychological tests and CSF and MRI biomarkers correctly predicted about two third of the conversion, and almost three quarters when combined, in the relatively young patients. Contrary to expectation, FDG-PET was only a marginally significant predictor in these patients. In the older patients neuropsychological assessment and MRI predicted conversion to some extent, but CSF biomarkers and FDG-PET did not. Again, the techniques combined predicted slightly better, but FDG-PET did not contribute to the prediction. The differences between the models were not significant. Supplementary Figure 1 (available online: http://www.j-alz.com/issues/29/vol29-3.html#supplementarydata05) shows the Receiver Operating Curves of significant predictors of conversion to AD in the old age cohort.

DISCUSSION

These results indicate that structural MRI and neuropsychological assessment retain their potential for predicting conversion from MCI to AD when applied in older patients, whereas CSF biomarkers lose this potential. This finding corroborates our analysis of the baseline ADNI data, in which we found the same age effect with respect to the diagnosis of prevalent AD and MCI [8]. Contrary to our expectation, FDG-PET lost its predictive potential even in the younger patients, while in the total sample it hardly increased the a priori classification success. Although statistically significant, the predictive performance of the other techniques was modest also. MRI and neuropsychological assessment increased the success rate with about 10 percent points (or about 20, if calculated optimistically), and CSF biomarkers with a similar degree in the younger patients only. In combination, these three techniques raised the success rate with about 15–25 percent points compared to the *a priori* success rate (Table 2). Apparently, it is very difficult to increase prognostic accuracy further with respect to progression to AD within a few years by the present diagnostic techniques, once a diagnosis of MCI has been established. A plausible explanation of this limited predictive success is that in patient samples like the present one, the very diagnosis of amnestic MCI already conveys an extremely high risk of conversion [21], in this case 46% in less than 3 years on average, leaving little room for improvement of prediction.

Examination of the effect of age on the diagnostic and predictive potentials of the techniques used in patients suffering from (incipient) dementia is important for several reasons. First, the vast majority of demented patients is older than 75 years [10], while much dementia research is being conducted in relatively young patients [22]. Second, after the age of 75 there is a clear increase in the prevalence of other brain diseases than AD that may contribute to dementia, in particular cerebrovascular disease and hippocampal sclerosis [11, 12]. Consequently, conclusions drawn from dementia research are not necessarily valid in clinical practice, unless age is taken into account.

Another, more theoretical implication of these findings is that the prevalence of AD in older age cohorts will probably be much lower than currently thought if CSF biomarkers are to play a prominent role in the definitions of the disease, as was recently proposed [23, 24]. Subjects with a dementia syndrome that clinically mimics AD, but who lack CSF or neuroimaging biomarker results typical of AD, will no longer be considered as suffering from AD. Conversely, given the low specificity of the CSF biomarker signature [25], there will be a large group of subjects with an abnormal CSF profile, who will never convert to dementia. In everyday practice, diagnostic difficulty will arise also in patients with a clinical syndrome not typical for AD, but with the CSF signature of AD. Especially classification of dementia syndromes in patients older than 75 years may be challenging, because most of these patients have multiple cerebral pathologies [11, 26].

Some techniques are invasive, some are expensive, and some are both. For clinicians it is important to be aware of any limitations in the applicability of such techniques, to enable them to make rational choices in the diagnostic work-up of their patients. Practical conclusions that clinicians may draw from the present and our earlier analyses are that FDG-PET and CSF

biomarkers are less informative in patients older than 75 years. These markers are not very useful with respect to the diagnosis of AD beyond this age, nor with respect to the prediction of conversion to AD within a few years. In younger patients, all four techniques are about equally informative (except FDG-PET for predicting conversion).

Furthermore, the order in which the diagnostic techniques are deployed is irrelevant from the perspective of increasing diagnostic information. For example, we examined whether it makes any difference to the final estimate of diagnostic accuracy if neuropsychological assessment is done first, and MRI and lumbar puncture second, or vice versa. This is not the case, however. The first technique deployed is the most informative, the second and third add only a little more to the diagnostic accuracy (data not shown). Therefore, practical considerations such as patient burden or costs associated with the respective diagnostic investigations, may determine the final choice for the most rational diagnostic algorithm.

A previous study on the ADNI sample reported conversion of 26% of MCI patients with abnormal CSF values versus 12% of MCI patients with normal CSF composition after about one year of follow-up [27]. Percentage of correct predictions was 43%. Our analysis was done at a mean of 2.7 years of follow-up, and the percentage of correct predictions based on CSF was higher (63%), probably due to disease progression. It is to be expected that this percentage will rise further, but the question is to what level, and whether it will also rise in the older half of the cohort. Among the CSF biomarkers only Aβ was a significant predictor of conversion in our analyses. This is in line with the hypothesis that amyloid accumulation occurs early in the disease course, whereas elevated CSF values of tau appear only later [17].

Of all neuropsychological variables only indices of memory performance were selected as significant predictors of conversion to AD. This is remarkable because in the ADNI sample MCI is practically synonymous to memory impairment (99% of MCI patients in ADNI have amnestic MCI). Thus, MCI was to a large degree defined by impaired performance on memory tests. Nevertheless, after MCI has been diagnosed, the same tests apparently continue to have at least as much additional prognostic information as MRI and CSF biomarkers. This corroborates the observation made in our meta-analysis of longitudinal MCI studies [7], but now based on a single, large data set. The meta-analysis also suggested that relatively weak memory performance of subjects who were cognitively normal at baseline to some extent predicted progression to AD many years later, a suggestion recently confirmed in an autopsy study [28].

Unlike other longitudinal studies on disease progression, we did not use Cox regression analysis to find significant predictors of conversion. We preferred to apply logistic regression because of three reasons. First, Cox regression would treat CSF biomarkers unfairly and favor the other techniques, because these latter techniques, unlike CSF biomarkers, yield more abnormal results when assessed closer to the moment of conversion. Second, Cox regression is used to find predictors of the moment when a particular event occurs (in this case conversion). In clinical practice, however, it is more important to know who will ultimately progress to AD than to know whether this will happen a few months earlier or later. The third reason why we chose logistic regression was that it allows statistical comparison of the resulting models by examination of the AUC confidence intervals of ROC analyses, which also lend themselves more easily to clinical interpretation.

The ADNI project is a major enterprise making very important contributions to AD research [29]. Nevertheless, the ADNI dataset has some limitations. One is that it is exclusively focused on the diagnosis of AD. However, in clinical practice other conditions such as depression or cerebrovascular disease are not excluded *a priori*, as is the case in the ADNI project. Consequently, the analyses in the present paper are somewhat artificial and do not reflect clinical reality, which often includes many differential diagnostic considerations. Second, about 50% of the participants consented to lumbar puncture. This reduced the sample size for the present analyses. Also PET scanning was applied in part of the sample, which further reduced the number of participants in the corresponding analyses ($n = 89$). This created a setback for PET compared to the other techniques. The present regression models involving PET scanning are therefore less stable than the other models.

In conclusion, ancillary investigations only modestly increase accuracy in predicting conversion from MCI to AD, and neuropsychological assessment and MRI variables predict conversion irrespective of age, while CSF biomarkers only do so in relatively young subjects. Thus, the present analysis adds to the growing body of evidence that populations fulfilling diagnostic criteria for MCI or AD are heterogeneous, and that age is an important characteristic of the underlying heterogeneity.

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