

Qualitative Estimates of Medial Temporal Atrophy as a Predictor of Progression From Mild Cognitive Impairment to Dementia

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Background: Individuals diagnosed as having mild cognitive impairment (MCI) have a high likelihood of progressing to dementia within 3 to 5 years, but not all individuals with MCI progress to dementia. Prognostic uncertainty suggests the need for additional measures to assist the clinician.

Objective: To assess the added value of qualitative measures of medial temporal atrophy (MTA) to estimate the relative risk of progressing from MCI to dementia.

Design: A 3-year, double-blind, placebo-controlled Alzheimer's Disease Cooperative Study initially designed to evaluate the efficacy of donepezil hydrochloride or vitamin E vs placebo to delay progression of MCI to dementia.

Setting: Memory assessment centers.

Patients: A total of 190 individuals with MCI.

Main Outcome Measures: Ratings of MTA performed using magnetic resonance images obtained at baseline. Log-rank tests and Cox proportional hazards ra-

tios examining the significance of MTA estimates in predicting progression of MCI to dementia.

Results: A mean MTA score greater than 2.0 was associated with a greater than 2-fold increased likelihood of progression to dementia during the observation period (hazards ratio, 2.30; 95% confidence interval, 1.09-4.92; $P=.03$) after controlling for age, education, sex, and baseline Mini-Mental State Examination score.

Conclusions: Adjusted estimates of MTA were associated with significantly increased risk of developing dementia within 3 years, suggesting that obtaining a magnetic resonance image during the evaluation of MCI may offer additional independent information about the risk of progression to dementia. Given the relatively high prevalence of MCI in the general population, use of this method as part of routine clinical evaluation may help identify individuals who might benefit from increased surveillance and future treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00000173.

Arch Neurol. 2007;64:108-115

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Group Information: A list of the Alzheimer's Disease Cooperative Study Group Investigators appears on page 114.

CLINICAL AND PATHOLOGICAL evidence indicates that older individuals who have significant memory impairment but are not demented may be in a transition phase between normal aging and Alzheimer disease (AD), often denoted as "amnesic mild cognitive impairment" (aMCI).¹⁻⁵ Patients with aMCI have a high likelihood of progressing to clinically probable AD within 3 to 5 years,^{1,6,7} and current American Academy of Neurology guidelines suggest careful monitoring of these individuals.⁸ The high population prevalence^{1,9} and clinical uncertainty of progression to dementia¹ suggest the need for additional measures to assist the clinician.⁸ Bedside

cognitive tests such as the Mini-Mental State Examination (MMSE)¹⁰ are relatively insensitive to early detection of high-risk individuals, and current guidelines suggest the use of detailed neuropsychological testing to determine actual risk.⁸ Neuropsychological testing procedures, however, are time-consuming, sensitive to extracerebral patient features (such as fatigue and pain), expensive, and not generally available to physicians practicing in a community setting.

Magnetic resonance imaging (MRI) is a commonly available tool with possible predictive value. Quantitative MRI studies suggest that hippocampal atrophy is present before dementia is clinically evident.¹¹⁻¹³ Prospective studies of patients

with aMCI¹¹ find a 4-fold increase in the percentage of individuals converting to dementia within 5 years when hippocampal size was 2.5 SDs below age- and sex-defined reference ranges.

These findings support the utility of brain imaging in aMCI to predict progression to AD. For this method to be applicable in clinical practice, however, a simple and convenient method for reliable and reasonably accurate estimates of hippocampal size is required. Two studies^{14,15} using qualitative estimates of hippocampal size showed considerable promise but were limited to small groups of patients with aMCI in a retrospective and unblinded manner. For this study we tested the predictive abilities of a simple and reliable scale¹⁶⁻¹⁹ on a subgroup of individuals enrolled in an ongoing therapeutic trial for aMCI.²⁰ This study examined the efficacy of using donepezil hydrochloride, 10 mg/d, or vitamin E, 2000 IU/d, to delay progression of aMCI to dementia compared with placebo across 3 years.²⁰ Compared with the placebo group, there were no significant differences in the probability of progression to dementia in the vitamin E group or the donepezil group at the end of 3 years of treatment. We hypothesize that qualitative estimates of medial temporal atrophy (MTA) would significantly increase the likelihood of identifying patients with aMCI at risk for converting to AD above conventional clinical practice, which includes the history, neurological examination, and MMSE. The absence of a significant treatment effect for the study allowed us to combine participants across treatment groups to assess the ability of MTA measures to predict progression of aMCI to dementia.

METHODS

PARTICIPANTS

The details of study rationale, design, and participant characteristics for the parent study and the MRI substudy have previously been described in detail.^{20,21} In brief, 769 participants were recruited from 69 Alzheimer's Disease Cooperative Studycenters in the United States and Canada. Enrollment was based on the criteria for aMCI as previously described,¹ modified to use the logical memory II subtest of the Wechsler Memory Scale-Revised,²² adjusted for educational achievement.²¹ Additional requirements included a Clinical Dementia Rating scale score of 0.5^{23,24} and insufficient cognitive or functional impairment to meet NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria for AD.²⁵ The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, and the US Code of Federal Regulations Title 21 Part 50 (Protection of Human Subjects) and Title 21 Part 56 (Institutional Review Boards). Written informed consent was obtained from all the participants and from study partners who had knowledge of the participants' functional activities. A data and safety monitoring board reviewed the blinded safety data every 3 months during the trial.

A subset of 195 individuals underwent a research brain MRI examination at entry to the study as part of an ancillary study.^{26,27} These individuals were selected solely on the basis of their willingness to participate and the availability of suitable MRI equipment at the clinical sites participating in the parent trial.

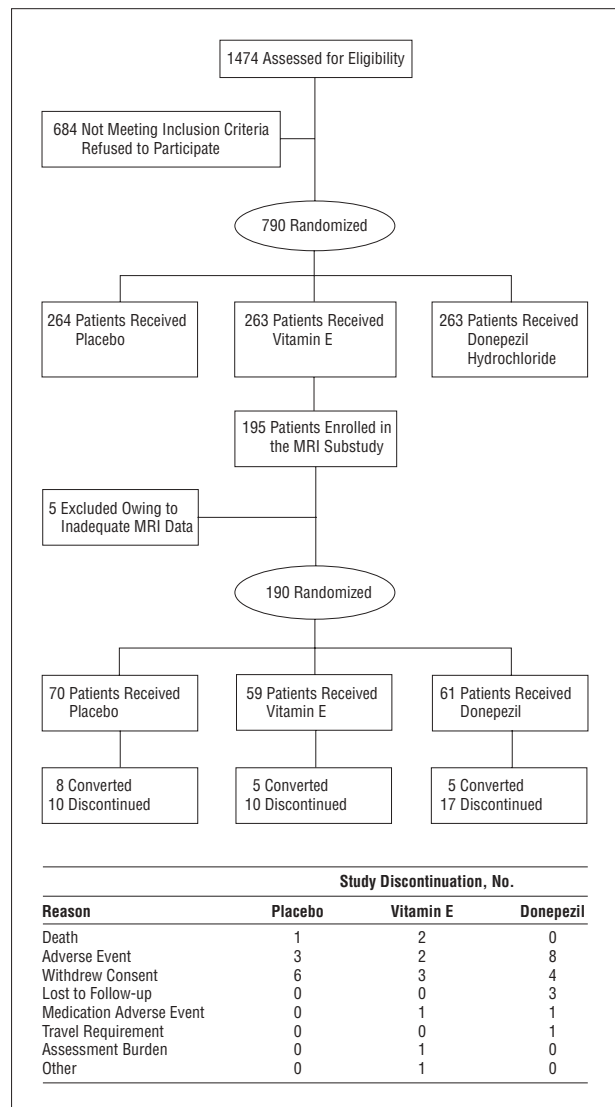


Figure 1. Flow diagram of the progress of participants through the parent clinical trial and the magnetic resonance imaging (MRI) substudy.

MRI ACQUISITION

The imaging protocol for this study included a T1-weighted, 3-dimensional, volumetric spoiled-gradient recalled echo sequence with 124 contiguous partitions, 1.6-mm section thickness, a 22.0 × 16.5-cm field of view, 192 views, and a 25° flip angle. The MRI data were transmitted from participating sites to a central data repository at the Mayo Clinic (C.R.J.), where imaging data were checked for compliance with the prescribed imaging sequences and then cataloged.

For this study, deidentified image data were transferred from the Mayo Clinic data repository to the Imaging of Dementia and Aging Laboratory at the University of California at Davis. Of the original 195 images, 5 were not read owing to technical difficulties, leaving a total of 190. Three additional individuals were lost to follow-up. Details of study participant recruitment, enrollment, and outcome are described in **Figure 1**.

QUALITATIVE ANALYSIS

The MRI analysis was restricted to MTA estimates of the MRI at the time of study enrollment. Each MRI was rated using a previ-

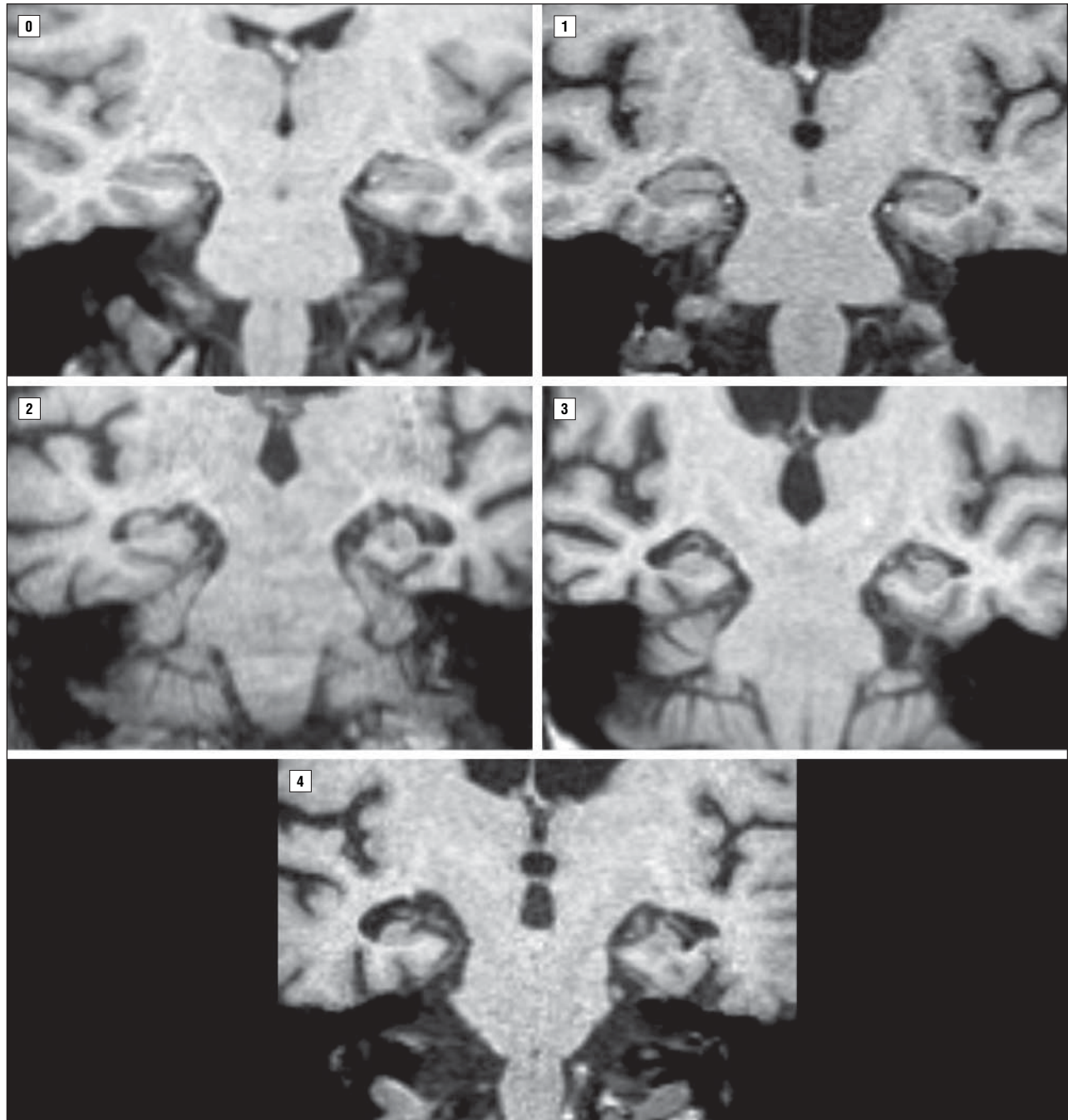


Figure 2. Representative magnetic resonance images used to determine medial temporal atrophy ratings. See Table 1 for complete descriptions of the ratings.

ously published qualitative rating scale¹⁶⁻¹⁸ that assesses the extent of MTA by estimating the combined widths of the choroidal fissure and the temporal horn of the lateral ventricle and the height of the hippocampus in the coronal oblique orientation to derive 1 score based on 5 different categories ranging from 0 (no atrophy) to 4 (severe atrophy) (**Figure 2** and **Table 1**). The right and left medial temporal structures were rated separately, and an overall estimate was created using the average of the 2 ratings. All the images were rated under conditions common to conventional clinical radiologic interpretation.

Four neurologists (C.D., G.B.F., C.M.C., and P.S.) with considerable experience in the clinical diagnosis of AD but with varying degrees of expertise in qualitative analysis of MRIs separately analyzed each MRI. All the ratings were performed with-

out clinical information (eg, age, sex, and progression status) other than the knowledge that they were enrolled in a clinical trial to study treatment of aMCI.

All the raters viewed coronal MRIs at 3× magnified view on video monitors attached to computer workstations (Ultra 5; Sun Microsystems Inc, Santa Clara, Calif) using locally developed viewing software that allowed the rater to view the image in a manner similar to that of a standard radiologic viewing console. Data were recorded directly into spreadsheet program (Excel 2000; Microsoft Corp, Redmond, Wash) files for analyses using statistical software (SAS Version 9; SAS Institute Inc, Cary, NC).

The MTA ratings proceeded in 3 consecutive steps. The first step consisted of an approximately 1-hour training session led

Table 1. Medial Temporal Atrophy Rating Algorithm

Score	Width of Choroidal Fissure	Width of Temporal Horn	Height of Hippocampus
0	Normal	Normal	Normal
1	Mildly widened	Normal	Normal
2	Moderately widened	Mildly widened	Mildly reduced
3	Markedly widened	Moderately widened	Moderately reduced
4	Markedly widened	Markedly widened	Markedly reduced

by one of us (P.S.) where the 3 other raters were instructed on use of the rating scale through shared review and rating of 35 deidentified images selected from the Imaging of Dementia and Aging Laboratory archives previously confirmed to vary widely in MTA. After completion of the training session, each rater independently rated a second and unique group of 50 deidentified images selected from the Imaging of Dementia and Aging Laboratory archives and confirmed to vary widely in MTA to test interrater agreement. After statistical analysis found satisfactory interrater agreement (see the "Results" section), the raters rated the 190 images that compose the data set for this study.

STATISTICAL ANALYSES

The interclass correlation coefficient, which estimates the variability of different ratings of the same individual to the total variation across all ratings and all individuals,²⁸ was used to assess the interrater reliability of the qualitative scale. The primary outcome for this analysis was time of progression to dementia associated with MTA scores obtained at the time of study enrollment. Kaplan-Meier curves were used to illustrate differences in the pattern of progression between those scoring 2.0 or less and those scoring greater than 2.0 on the scale based on previous evidence that a score of 3.0 or higher is consistent with AD.¹⁶ A second analysis based on modified criteria previously reported²⁹ also evaluated the patterns of progression based on MTA scores between 0 and 1.0 and those greater than 1.0. The results for each rater were examined separately as was a summary analysis using the mean qualitative rating score from the 4 raters. Because dichotomized measures based on MTA scores were used for the evaluation of clinical efficacy, we also computed κ statistics for the group using MTA cutoff scores of 1.0 and 2.0.³⁰ To evaluate the added independent effects of MTA measures, Cox proportional hazards models with MMSE were fit separately, followed by models with both MMSE and MTA measures. The independent effects of treatment and apolipoprotein E genotype on conversion to dementia were also examined in separate analyses. These models were used to assess the association of the dichotomized qualitative score with time to progression to dementia after adjusting for age, sex, education, and MMSE score.³¹ Sensitivity, specificity, and positive and negative predictive values were also determined for MTA.

RESULTS

INTERRATER RELIABILITY

Interclass correlation coefficients for interrater reliability were calculated in 2 ways. First, each of the 3 less experienced raters was individually compared with the developer of the scale (P.S.) on right, left, and mean MTA scores. Interclass correlation coefficients for each rater pair were consistently greater than 0.82 and varied between 0.82 and

Table 2. Demographics of the Study Participants*

Variable	Converted to Dementia (n = 66)	Did Not Convert (n = 121)	Total (N = 187)†
Age, y	73.7 ± 7.0	72.3 ± 6.5	72.8 ± 6.7
Education, y	15.0 ± 3.1	15.0 ± 2.8	15.0 ± 3.0
Male sex, %	51.5	57.0	55.1
Hippocampal rating‡	1.15 ± 0.75	0.84 ± 0.59	0.95 ± 0.67

*Data are given as mean ± SD except where noted otherwise.

†Three participants were missing conversion status.

‡Mean of all 4 raters.

0.86. Second, all the raters were compared as a group. There was moderate to substantial agreement,³² with interclass correlation coefficients of 0.81, 0.78, and 0.82 for right, left, and mean MTA scores, respectively. In addition, there was little variation across the raters despite differences in experience with the qualitative rating procedure. Group κ statistics³⁰ were also calculated using MTA scores of 1.0 and 2.0. Moderate agreements³² of 0.53 and 0.47 were found for the group using MTA cutoff scores of 1.0 and 2.0, respectively. Raters rarely differed by more than 1 category of MTA score, and there were no systematic differences among the raters.

PARTICIPANTS

Of the 190 MRIs with data available, progression data were available for 187. Demographics of the individuals studied are summarized in **Table 2**. Mean age, education, and sex distributions for this subsample were similar to those of the parent study,^{20,21} where the mean ± SD age was 72.9 ± 7.3 years, the mean ± SD educational achievement was 14.7 ± 3.1 years, and women made up 45.8% of the sample. Baseline mean ± SD MMSE scores were nearly identical between the parent study (27.3 ± 1.8) and the MRI substudy (27.5 ± 1.8). Randomization by treatment arm for this subset of individuals was also nearly identical, with 32.1% randomized to donepezil, 31.1% to vitamin E, and 36.8% to placebo. A total of 66 participants (33.7%) in the MRI group progressed to dementia during the 3-year observation period. After adjusting for person-years of observation, this resulted in a 16.1% yearly rate of progression to dementia for the group, nearly identical to that of the full cohort from the parent study.²⁰

Participants who progressed to dementia were older than those who remained at aMCI throughout the study but had similar educational achievement and sex distributions (Table 2). Participants who progressed to dementia had significantly higher mean ± SD MTA ratings than did those maintaining an aMCI diagnosis (1.15 ± 0.75 vs 0.84 ± 0.59; $P = .002$), indicating greater MTA atrophy at the time of enrollment in the study. Mean ± SD MMSE scores were significantly lower at baseline for patients who progressed to dementia (26.8 ± 1.86 vs 27.9 ± 1.70; $P < .001$). The MTA ratings also significantly correlated with MMSE scores ($r = -0.20$; $P = .005$). Alzheimer disease was the clinically determined cause of dementia at

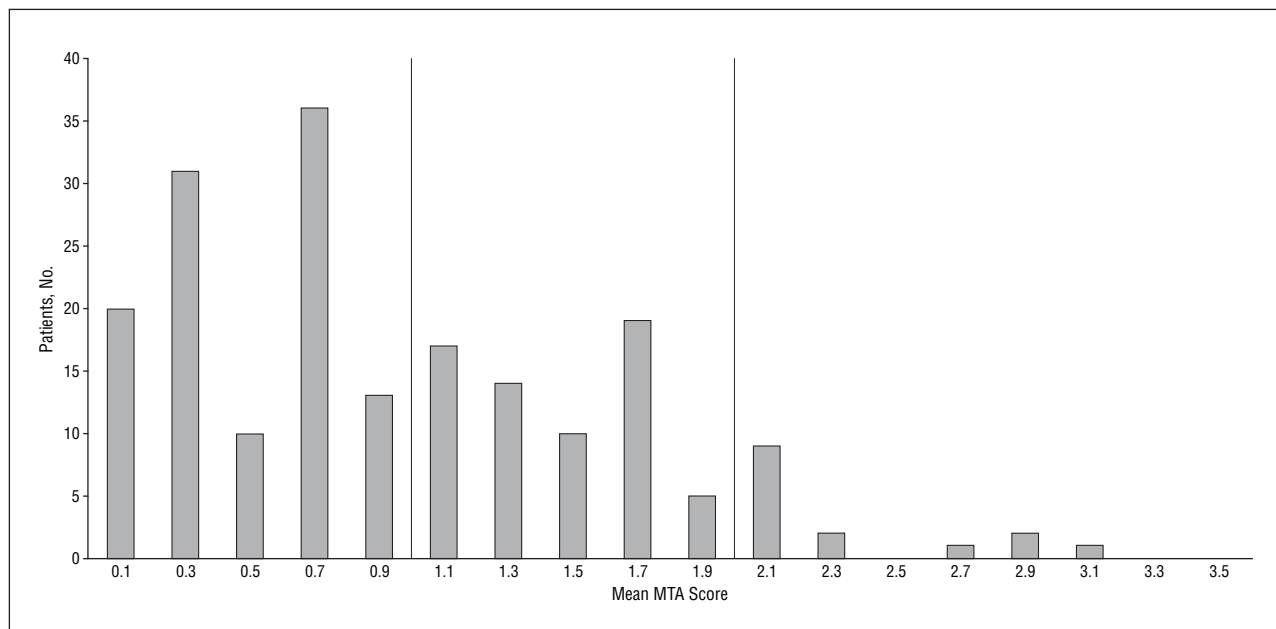


Figure 3. Distribution of mean medial temporal atrophy (MTA) ratings for the 190 study participants. Seventy-nine patients (41.6%) had MTA scores of 1.0 or greater, and 15 patients (7.9%) had scores of 2.0 or greater.

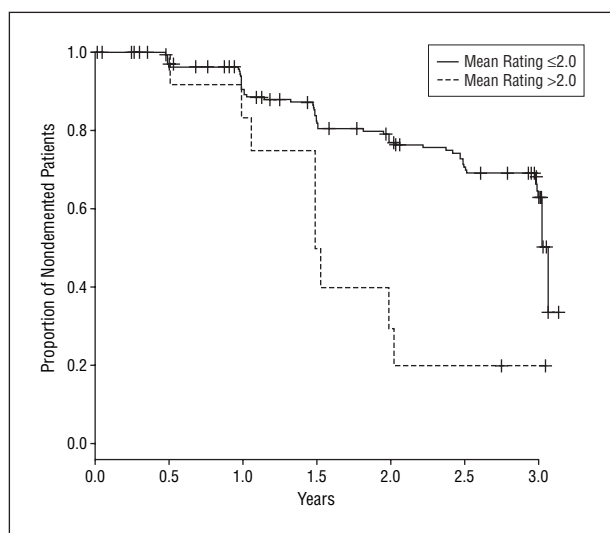


Figure 4. Kaplan-Meier curves for participants with medial temporal atrophy ratings of 2.0 or less compared with those with ratings greater than 2.0.

the time of dementia diagnosis for 99.0% of the study participants.²⁰

DISTRIBUTION OF MTA RATINGS WITH aMCI

The distribution of ratings is graphically illustrated in **Figure 3** and varied from 0 to 4 for the individual raters. Consistent with previous qualitative ratings of patients with aMCI,¹⁵ no subject consistently received a rating of 4 across all raters, limiting the maximal average rating to 3.1. Only 15 subjects (7.9%) had a mean MTA score greater than or equal to 2.0, and only 12 (6.3%) had a mean MTA score greater than 2.0, indicating that severe MTA¹⁵⁻¹⁸ was uncommon, whereas 79 subjects (41.6%) had a mean MTA

score greater than or equal to 1.0 and 70 (36.9%) had a mean MTA score greater than 1.0.

MTA AND PROGRESSION TO DEMENTIA

As noted in the “Participants” subsection, the overall progression to dementia was 33.7% during the 3 years of the study. Increasing MTA ratings were associated with an increasing percentage of individuals progressing to dementia. For individuals with a mean rating of 1.0 or less, only 29.1% progressed to dementia, whereas for those with a mean rating greater than 1.0, 45.7% progressed to dementia; for 2.0 or greater, 60.0% progressed to dementia; and for greater than 2.0, 75% progressed to dementia.

KAPLAN-MEIER CURVES

Kaplan-Meier curves were used to illustrate progression patterns according to MTA ratings where substantial atrophy was defined as an MTA score greater than 2.0 for the mean of the group ratings (**Figure 4**). Individuals with MTA scores greater than 2.0 had a hazards ratio (HR) of converting to dementia that was 2.30 (95% confidence interval, 1.09-4.92) times that of an individual with more modest atrophy ($\beta=0.84$; $SE=0.38$; $P=.03$) after adjusting for age, education, sex, and baseline MMSE performance. Similar analyses using MTA scores greater than 1.0 revealed an HR of converting that was 2.30 (95% confidence interval, 1.33-4.08) times that of an individual with more modest atrophy ($\beta=0.84$; $SE=0.29$; $P=.003$).

The MMSE scores were also significantly associated with increased likelihood for progression from aMCI to dementia. After adjusting for age, education, and sex, a difference of a 1-U increase in the MMSE score was associated with a 25% reduction in the likelihood of progression to dementia ($\beta=-0.31$; $SE=0.08$; $P<.001$; HR, 0.73; 95%

confidence interval, 0.63-0.85). The inclusion of MMSE scores in the analysis only marginally reduced the HR of MTA ratings on predicting progression.

The effects of treatment group and apolipoprotein E genotype were also separately evaluated. Including treatment group in the analysis with age, education, and sex did not substantially change the HR of converting to dementia using MTA cutoff scores of 1.0 (HR, 2.64; $P < .001$) and 2.0 (HR, 3.14; $P = .003$). Including apolipoprotein E genotype in the analysis marginally reduced the HR of converting to dementia using MTA cutoff scores of 1.0 (HR, 2.34; $P = .003$) and 2.0 (HR, 2.44; $P = .02$).

Table 3 summarizes individual performance using unadjusted MTA cutoff scores of 1.0 and 2.0. The ability of the individual raters to predict progression to dementia was generally significant but somewhat variable. Using a cutoff score greater than 2.0, HRs varied from 2.0 to more than 5.0 but were less consistent among raters, whereas using a cutoff value greater than 1.0 we found more similarity in the group and closer correlation with the group mean measure. These differences likely reflect variability among raters for the relatively small number of MTA scores greater than 2.0.

SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES

Sensitivity, specificity, and positive and negative predictive values can be used to estimate the added value of MTA ratings in addition to the clinical designation of aMCI. Using a cutoff MTA score greater than 2.0, sensitivity was 14%, specificity was 98%, the positive predictive value was 75%, and the negative predictive value was 69%. Using a cutoff MTA score greater than 1.0, sensitivity was 51%, specificity was 69%, the positive predictive value was 46%, and the negative predictive value was 73%. These results support the observation that many fewer individuals with low MTA scores (≤ 1.0) progressed to dementia (29.1%) compared with the 60.0% with MTA scores of 2.0 or greater or the 45.7% with scores greater than 1.0.

COMMENT

These results suggest that estimates of MTA convey added value to routine clinical evaluation of individuals with aMCI most likely to progress to dementia within 3 years. Although previous studies^{14,15} have reported similar results, to our knowledge this is the first such study to evaluate the added impact of MTA ratings in a prospective and blinded manner.

The predictive power of these results is also comparable to previously reported quantitative analyses. For example, in 1 study¹¹ an HR of 1.45 was reported for each 1-U decrease in the hippocampal W score (increase in atrophy) for progression to AD. This suggests that quantitative and qualitative ratings of MTA may have similar abilities to predict outcome in patients with aMCI. Qualitative ratings, however, have the additional advantage of being easy to perform in the clinical setting while retaining high interrater agreement.

Table 3. Impact of Individual Ratings of MTA

Rater No.	MTA Score >1.0		MTA Score >2.0	
	HR (95% CI)	P Value	HR (95% CI)	P Value
1	2.10 (1.28-3.47)	.004	3.59 (1.85-6.96)	<.001
2	1.87 (1.13-3.08)	.02	2.96 (1.17-7.47)	.02
3	2.28 (1.28-4.04)	.005	5.86 (1.80-19.16)	.003
4	2.33 (1.41-3.84)	<.001	2.01 (0.80-5.05)	.14

Abbreviations: CI, confidence interval; HR, hazards ratio from the Cox proportional model; MTA, medial temporal atrophy.

The present results might also benefit the clinical evaluation of patients with memory complaints that may or may not meet the strict criteria for aMCI. Complaints of memory impairment are common in the elderly,³³ making it difficult to distinguish the very earliest features of AD from other disorders. Epidemiologic studies^{1,9} also suggest that aMCI is relatively common, with a prevalence of 3% among individuals 65 years and older. Because AD is associated with increased health care costs^{34,35} and current treatments are known to be clinically effective even when the disease is mild,³⁶ the ability to distinguish individuals at greatest risk for future dementia from the host of individuals visiting a clinical practice with memory complaints is likely to result in public health benefits through increased monitoring, education, and timely treatment.

Although this study focused on a highly select group of individuals who met strict research criteria for aMCI, these results may still translate well into clinical practice where subjective memory complaints are common, but the time and resources to adequately evaluate these common complaints are limited. Sensitivity and specificity are also important. In this regard, use of a high MTA cutoff score, such as greater than 2.0, although infrequent in this study, was associated with a high rate of progression to dementia (75.0%) and a specificity of 98%, which compares favorably with quantitative measures of the hippocampus.^{11,26} Although relatively insensitive, the high specificity of this measure is ideal for application to general clinical practices that favor a more conservative approach.

The strengths of this study include the blinded prospective nature of the study design, inclusion of a well-defined patient cohort, and detailed surveillance by physicians with dementia experience. In addition, the method used is simple, has good reliability, and could be easily translated into standard clinical practice. Weaknesses of this study include the select nature of the study cohort, which included well-educated individuals who had moderately severe episodic memory impairments and a clinical course suggestive of early AD.⁵ In addition, the present results indicate that experience in using the scale may have a modest effect on the predictive value of the scale, particularly when using a cutoff score greater than 2.0. At least some of the differences among the raters reflect the study design, which included only a few participants ($n = 15$) with mean MTA scores greater than 2.0, thereby exacerbating differences in outcome with only small differences in ratings.

In conclusion, these data show that use of a relatively simple, clinically applicable MTA rating scale significantly increases the likelihood of identifying individuals with aMCI who are destined to progress to dementia within 3 years above standard clinical evaluation, which includes MMSE testing. The method is easy to use and reliable, characteristics that offer the potential for use in routine clinical practice. Given the increasing prevalence of AD in our aging society³⁷ and the potential benefits of early diagnosis and treatment of AD,³⁸ we believe that this approach may be useful for identifying patients with aMCI at high risk for progression to AD.

Accepted for Publication: July 28, 2006.

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Financial Disclosure: This study was conducted independent of any pharmaceutical company sponsorship. Dr DeCarli is a consultant to Eisai Pharmaceuticals and has received research support from Eisai and Genzyme Pharmaceuticals. Dr Thal is a consultant to Amgen, Avera, Elan, Lilly, Merck, Rinat, Sanofi, Toyama, Acumen, and Ceregene Pharmaceuticals. Dr Petersen is a consultant to Elan and Sevier Pharmaceuticals and has received educational grants from Pfizer, Eisai, Novartis, and Janssen Pharmaceuticals. Dr Frisoni has received honorarium from Pfizer, Novartis, Bracco, and Janssen Pharmaceuticals.

Funding/Support: This study was supported by grants 990802 and 2002073 from the Institute for the Study of Aging and by grants NIA P30 AG10129 and NIA U01-10483 from the National Institutes of Health.

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Announcement

Calendar of Events: A New Web Feature

On the new Calendar of Events site, available at <http://pubs.ama-assn.org/cgi/calendarcontent> and linked off the home page of the *Archives of Neurology*, individuals can now submit meetings to be listed. Just go to <http://pubs.ama-assn.org/cgi/cal-submit/> (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.

fore the clinical onset of ALS, such as dietary habits, occupation, and whether the patient served in a war.

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Financial Disclosure: None reported.

1. Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower disease progression and prolonged survival in contemporary patients with amyotrophic lateral sclerosis: is the natural history of amyotrophic lateral sclerosis changing? *Arch Neurol.* 2006;63:1139-1143.
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In reply

We thank Drs Kano, Arasaki, Ikeda, and Iwasaki for their comments on our study.¹ It is gratifying that in a Japanese population of patients with ALS, these investigators reached the same conclusion we had reached, namely that contemporary patients appear to have slower disease progression than patients seen prior to the year 2001. Even the diagnostic delay noted in the contemporary Japanese population is in accord with this conclusion. In a previous publication, we noted that one of the key factors influencing

survival in our ALS population was the delay in referral to our ALS clinic.² The greater the delay, the longer the survival. This finding was possibly related to the fact that patients with slow moving disease were more likely to delay visits to our clinic. In a more recent study, we were able to demonstrate that the diagnostic delay (measured as the time between first symptom and first examination) influenced disease progression as well as survival. We noted that patients with ALS examined by us for the first time more than 12 months after their first symptoms progressed more slowly than patients first examined less than 12 months after their first symptoms.³ The key question is how to explain this recent change in rate of progression and survival. None of the factors we examined provided a convincing answer, but we would agree that life style and/or environmental changes are likely candidates and merit detailed study.

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Financial Disclosure: None reported.

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Correction

Error in Abstract. In the Original Contribution titled "Qualitative Estimates of Medial Temporal Atrophy as a Predictor of Progression From Mild Cognitive Impairment to Dementia," published in the January issue of the ARCHIVES (2007;64:108-115), an error occurred in the abstract on page 108. In the last item of the abstract, the trial registration identifier should have been listed as NCT00000173. The online versions of this article on the Archives of Neurology Web site are correct.