Mild Cognitive Impairment Due to Alzheimer Disease is Less Likely Under the Age of 65

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Abstract: Patients with amnestic mild cognitive impairment (aMCI) are considered to have a high risk for Alzheimer dementia (AD). Even high positive predictive values, however, cannot be guaranteed even by tests with high sensitivity and specificity when disease prevalence is low. If we regard the clinical criteria for aMCI as a test for predicting aMCI due to AD, the positive predictive value of the criteria will be low by definition in young patients with aMCI (age below 65 years) because of the low prevalence of AD in this age group. To test this hypothesis, we compared CSF biomarkers for AD between young (age below 65 years) and old (age 65 years or older) age groups of normal cognition, aMCI, and AD of the Alzheimer's Disease Neuroimaging Initiative database. Using these biomarkers, we observed that the prevalence of aMCI due to AD differed significantly between the young and the old. For example, only 28.2% young aMCI, but 63.2% old aMCI, had abnormal CSF amyloid measures consistent with AD pathology. As posited, the presence of aMCI due to AD was lower in young aMCI than in old aMCI. Given that the likelihood of aMCI due to AD is reduced in younger subjects, more attention to and evaluation of alternative diagnoses need to be considered in this group.

Key Words: Alzheimer disease, amnestic MCI, CSF biomarkers for AD, aMCI in younger age, positive predictive values

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Patients with amnestic mild cognitive impairment (aMCI) are considered to be at high risk for Alzheimer disease (AD).[1] It is reported that 10% to 15% patients per year with aMCI will convert to AD and up to 80% within 6 years.[2,3] Recent studies have aimed to better identify the presence of AD in this group for early therapeutic or preventive medications.[4,5]

Cerebrospinal fluid (CSF) biomarkers have both diagnostic and predictive value for AD.[4–8] A reduced CSF level of amyloid-β peptide, amino acids 1-42 ($A\beta_{1\text{-}42}$) reflects amyloid deposition in the brain.[9] An increased CSF level of total tau (t-tau) and tau phosphorylation at threonine 181 ($p\text{-}tau_{181}$) indicates neuronal damage.[10] In particular, p-tau181 is specific to AD neuronal damage and can be used to discriminate AD from other central nervous system diseases such as acute stroke.[11,12] According to the Dominantly Inherited Alzheimer Network study, these changes in CSF biomarkers start 15 to 25 years before the onset of AD symptoms.[13] Therefore, $A\beta_{1\text{-}42}$, t-tau, and $p\text{-}tau_{181}$ are likely to identify the presence of AD pathology in patients with aMCI.[14]

However, there remain several obstacles to the routine use of biomarkers in the diagnosis of aMCI. aMCI defined by clinical criteria includes heterogenous groups[14,15] and, therefore, biomarkers may be required to confidentially identify the disease etiology. However, the intercenter variability in CSF $A\beta_{1\text{-}42}$ measurement is quite large.[16] Moreover, CSF is invasive and has associated complications.[17,18] Although amyloid imaging is an alternative approach, cost and availability limit the wide application at this time.[19,20] Therefore, clinical criteria remain the mainstay for diagnosis of aMCI, although the research criteria for aMCI supported by analysis of biomarkers, that is, the criteria for "aMCI due to AD," are important for identification of the underlying pathologies.[14]

When interpreting the results of tests or diagnosis, we should consider the prevalence of a disease,[21] that is, the positive predictive value (PPV) of a test increases as the prevalence increases. For example, if there is a diagnostic tool with 99% sensitivity and 99% specificity, its PPV for a

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disease with 30% prevalence is 97.7%. However, the PPV of the same diagnostic tool for a disease with 0.1% prevalence is only 9.0%. Similarly, if the clinical criteria for aMCI are used as a predictive tool for aMCI due to AD or, eventually, for AD converters, clinicians should consider the prevalence of subgroups of patients.

The prevalence of AD increases with increasing age.[22] After 65 years of age, the prevalence doubles every 5 years. The prevalence of late-onset dementia (aged above 65 y) is 6.4%,[23] whereas that of early-onset dementia (aged 20 to 64 y) has been estimated to be as low as 0.1%.[24,25] The prevalence of early-onset aMCI due to AD would be similar to that of early-onset AD, meaning that the PPV of the clinical criteria for diagnosis of early-onset aMCI will be low. In addition, there is discrepancy of the prevalence between clinically diagnosed MCI and AD, especially in the group aged below 65 years. The prevalence of clinically diagnosed aMCI is as much as 0.5% to 31.9%.[15] The prevalence of aMCI did not increase according to age.[15,26–28] Therefore, much of clinically diagnosed aMCI in patients under the age of 65 might have pathologies other than AD. However, the diagnosis of aMCI is made in clinical practice without regard to prevalence. To our knowledge, the impact of a low prevalence of aMCI due to AD among younger individuals has not been investigated. In this study, we aimed to compare the proportions of aMCI due to AD, determined by CSF biomarkers, in patients with clinically diagnosed aMCI grouped according to age.

METHODS

Participants

This study included 222 individuals with normal cognition (NC), 454 with aMCI, and 128 with AD, for whom data on CSF biomarkers at the baseline visit was available in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The definition of NC was as follows: no memory complaints and normal objective memory performance, Mini-Mental State Exam (MMSE) scores 24 to 30, and a clinical dementia rating (CDR) scale score for memory of 0. The patients with aMCI met the criteria proposed by Petersen et al.[2] They had MMSE scores of 24 to 30 and a memory CDR score of at least 0.5. Patients with AD met the "probable" criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[29] Because the ADNI includes only early stages of AD, the patients in our study with AD had MMSE scores of 20 to 26 and a sum-of-box CDR of 1 to 9. Demographic data including age, sex, years of education, and *APOE* ϵ4 status for the 3 groups are summarized in Table 1. There were many instances of missing data for the age at onset of disease. Therefore, we divided the patients with NC, aMCI, and AD into groups according to their age at the baseline visit of the study. For our study, we defined "young" and "old" as patients below 65 years of age and patients aged 65 years or above, respectively. The only significant difference between the young and old aMCI was the sex ratio.

ADNI

The ADNI was launched in 2003 by the US National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron-emission tomography, 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 to lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD (San Francisco VA Medical Center and University of California San Francisco). ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects, but ADNI has been followed by ADNI-GO and ADNI-2. To date, these 3 protocols have recruited over 1500 adults, aged 55 to 90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late aMCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed up in ADNI-2. For up-to-date information, see http://www.adni-info.org.

CSF Biomarkers and Their Signatures for AD

The concentrations of CSF proteins, $A\beta_{1\text{-}42}$, t-tau, and p-tau_{181} were assessed using the multiplex xMAP Luminex platform (Luminex Corp., Austin, TX) and Innogenetics/Fujirebio AlzBio3 immunoassay kits (Innogenetics, Ghent, Belgium).[30] The detailed methods for lumbar punctures and CSF protein analysis are described on the ADNI Web site (http://adni.loni.usc.edu/). We used the levels of CSF proteins at the baseline visit of participants. We regarded $A\beta_{1\text{-}42} < 192$ pg/mL, t-tau > 93 pg/mL, p-$tau_{181} > 23$ pg/mL, t-tau/$A\beta_{1\text{-}42} > 0.39$, or p-$tau_{181}$/$A\beta_{1\text{-}42} > 0.1$ as the CSF signatures for AD.[4]

Statistical Analyses

Differences in demographic factors between young and old groups of NC, aMCI, and AD patients were evaluated using the Student *t* test, the Pearson χ^2, or the Fisher exact test. $A\beta_{1\text{-}42}$, t-tau, p-tau_{181}, t-tau/$A\beta_{1\text{-}42}$, and p-tau_{181}/$A\beta_{1\text{-}42}$ were compared between young and old groups of NC, aMCI, and AD patients by analysis of covariance, adjusting for sex and years of education. Multiple logistic regression analyses were used to analyze the difference in CSF signatures for AD between age groups, adjusting for sex and years of education. The statistical analyses were performed using commercially available software (PASW for Windows, version 20.0; IBM Inc., Armonk, NY). A P value < 0.05 was considered to indicate statistical significance. Smoothing for nonparametric regression and density estimation of $A\beta_{1\text{-}42}$ were performed using the "sm" package of R (version 3.0.1).[31]

RESULTS

CSF Signatures for AD According to Age Group

We compared the concentrations of CSF biomarkers and percentage of CSF signatures for AD between young

TABLE 1. The Characteristics of Study Participants

	NC			aMCI			AD		
	Young (N = 6)	Old (N = 2 16)	*P*	Young (N = 78)	Old (N = 376)	*P*	Young (N = 20)	Old (N = 108)	*P*
Age (y)	62.5 ± 5.5	75.1 ± 5.2	< 0.001	60.9 ± 2.8	74.9 ± 5.8	< 0.001	60.2 ± 3.3	77.3 ± 6.0	< 0.001
Women (%)	50.0	48.1	1.000	57.7	36.7	0.001	50.0	38.9	0.353
Education (y)	16.8 ± 2.4	16.1 ± 2.8	0.534	16.3 ± 2.5	15.8 ± 2.9	0.221	16.3 ± 3.3	15.1 ± 3.3	0.052
APOE ϵ4 (%)	N = 6	N = 214	0.666	N = 76	N = 368	0.882	N = 20	N = 107	0.576
Heterozygote	33.3	19.6		38.2	38.9		40.0	47.7	
Homozygote	0.0	2.8		7.9	9.5		30.0	19.6	
Logical memory II									
Immediate	15.0 ± 3.2	13.9 ± 3.3	0.546	9.4 ± 3.4	8.4 ± 3.5	0.039	4.0 ± 3.1	4.0 ± 3.0	0.706
Delayed	12.2 ± 3.2	13.1 ± 3.3	0.362	6.9 ± 3.5	5.7 ± 3.3	0.012	1.5 ± 1.5	1.1 ± 1.8	0.747
RAVLT									
Immediate	49.2 ± 11.9	43.7 ± 9.2	0.180	39.9 ± 12.3	33.0 ± 9.5	< 0.001	23.4 ± 8.3	23.3 ± 7.5	0.757
Delayed	4.5 ± 1.9	5.9 ± 2.3	0.137	5.0 ± 2.8	4.0 ± 2.5	0.025	2.3 ± 2.3	1.8 ± 1.8	0.369

The data are presented as mean ± SD or percentile.
We divided young and old groups by age at 65 years.
APOE ϵ4 genotyping data were missing for 2 old NC, 2 young aMCI, 8 old aMCI, and 1 old AD.
AD indicates Alzheimer Disease; aMCI, amnestic mild cognitive impairment; NC, normal cognition; RAVLT, ray auditory verbal learning test.

and old aMCI (Table 2). Levels of $A\beta_{1\text{-}42}$, t-tau, p-tau_{181}, and t-tau/$A\beta_{1\text{-}42}$ differed significantly between young and old aMCI, as did the 5 CSF signatures for AD. The data for NC and AD patients were also included to identify the influence of AD pathology in the young groups. The levels of CSF biomarkers and the CSF signatures for AD show no differences between age groups for NC and AD patients. Similarly, the values of p-tau_{181}/$A\beta_{1\text{-}42}$ did not differ between any disease groups.

Figure 1 shows the % prevalence of amyloid burden ($A\beta_{1\text{-}42}$ < 192 pg/mL) according to the 5-year age blocks. In aMCI, the presence of amyloid burden is lower in groups under the age of 65. In AD, the percentage of amyloid burden is 100% in groups under the age of 70. In NC, the presence of amyloid burden progressively increases with increasing age. Paradoxically, only 58.3% of patients with AD (7/12) in the oldest age group (aged 85 years or older) had evidence of significant amyloid burden.

Distribution of CSF $A\beta_{1\text{-}42}$ Density in NC, aMCI, and AD

Figure 2 shows the density plots of $A\beta_{1\text{-}42}$ concentration according to disease group (Fig. 2A) or age group (Fig. 2B). A homogenous group may have a normal distribution, whereas a heterogenous group with 2 independent characteristics may show a combined distribution of 2 normal distributions. Patients with AD show a unimodal normal distribution, whereas those with NC have a bimodal distribution. The smaller peak of NC, which is similar to that of AD, may represent the high-risk group for AD, whereas the larger peak may represent those at low risk for AD. Patients with aMCI also show a bimodal distribution, with a reverse trend to that of NC: the larger peak of aMCI was similar to that of AD and the smaller peak was similar to the larger peak of NC. Density plots of young and old aMCI are shown to clarify the main constituents of the groups (Fig. 2B). Both groups show bimodal distributions.

TABLE 2. The Results of CSF Biomarkers According to Age Group

	NC			aMCI			AD		
CSF proteins	Young (N = 6)	Old (N = 216)	*P*	Young (N = 78)	Old (N = 376)	*P*	Young (N = 20)	Old (N = 108)	*P*
By absolute values									
$A\beta_{1\text{-}42}$ (pg/mL)	235.7 ± 78.3	218.7 ± 64.5	0.570	230.1 ± 69.9	186.7 ± 70.3	< 0.001	133.3 ± 20.3	146.8 ± 45.8	0.121
t-tau (pg/mL)	56.2 ± 24.9	71.6 ± 32.0	0.235	74.3 ± 45.7	98.2 ± 59.4	< 0.001	145.4 ± 68.0	117.8 ± 56.9	0.115
p-tau_{181} (pg/mL)	15.7 ± 4.3	23.3 ± 12.0	0.124	24.8 ± 15.5	30.3 ± 16.4	0.003	44.3 ± 18.8	39.0 ± 18.9	0.185
t-tau/$A\beta_{1\text{-}42}$	0.26 ± 0.12	0.38 ± 0.27	0.286	0.40 ± 0.39	0.66 ± 0.58	< 0.001	1.08 ± 0.52	0.88 ± 0.48	0.079
p-tau_{181}/$A\beta_{1\text{-}42}$	0.08 ± 0.04	0.13 ± 0.11	0.283	0.14 ± 0.13	0.17 ± 0.61	0.576	0.34 ± 0.17	0.30 ± 0.18	0.185
By cutoff* (%)									
$A\beta_{1\text{-}42}$ < 192 pg/mL	16.7	34.7	0.382	28.2	63.2	< 0.001	100.0	88.0	0.998
t-tau > 93 pg/mL	0.0	21.6	0.999	22.4	39.4	0.003	73.7	63.2	0.389
p-tau_{181} > 23 pg/mL	0.0	35.8	0.999	35.9	59.6	< 0.001	90.0	82.4	0.588
t-tau/$A\beta_{1\text{-}42}$ > 0.39	16.7	32.9	0.443	28.9	59.3	< 0.001	94.7	86.8	0.434
p-tau_{181}/$A\beta_{1\text{-}42}$ > 0.1	16.7	43.3	0.224	35.9	66.5	< 0.001	95.0	91.7	0.621

We divided young and old groups at the age of 65 years. $A\beta_{1\text{-}42}$ was missing in 1 old NC and p-tau_{181} was missing in 1 old aMCI.
t-tau was missing in 3 old NC, 2 young aMCI, 5 old aMCI, 1 young AD, and 2 old AD.
*We adopted the cutoff level for the CSF signature for AD as defined in the study by Shaw et al.[4]
AD indicates Alzheimer Disease; aMCI, amnestic mild cognitive impairment; NC, normal cognition; RAVLT, ray auditory verbal learning test.

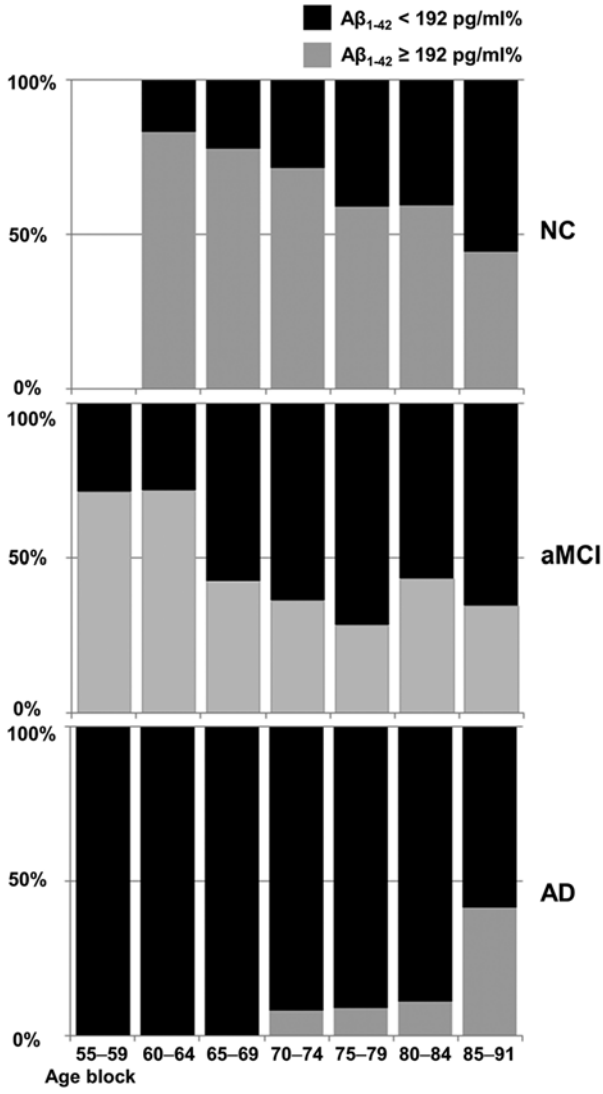

FIGURE 1. The % prevalence of amyloid burden ($A\beta_{1\text{-}42} < 192$ pg/mL) according to 5-year age blocks. Detailed data are shown in the Supplementary Digital Content 1, http://links.lww.com/WAD/A95.

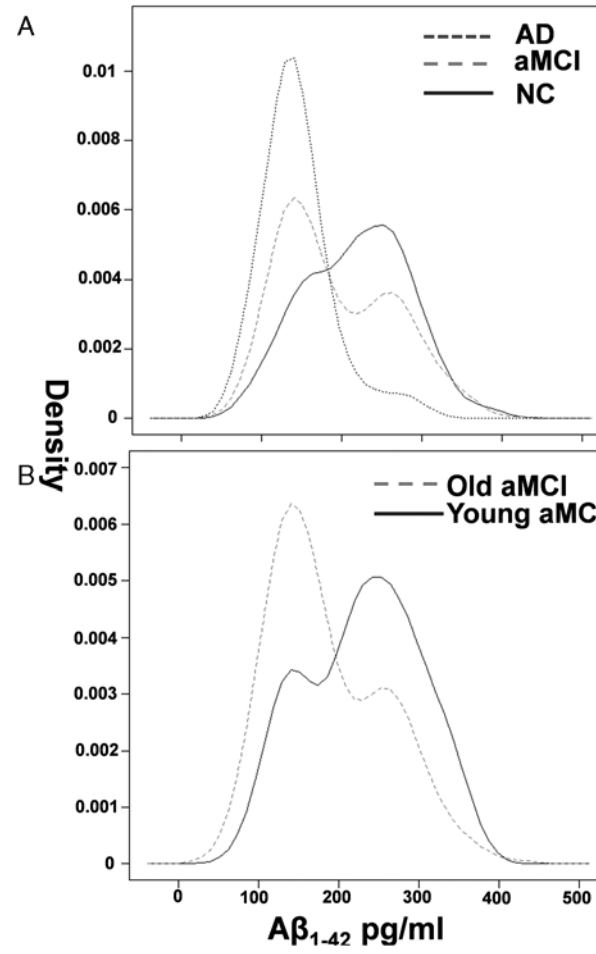

FIGURE 2. Density plots of $A\beta_{1\text{-}42}$. A, Density plots for NC, aMCI, and AD. B, Density plots for young and old aMCI. We divided young and old groups at the age of 65 years. AD indicates Alzheimer Disease; aMCI, amnestic mild cognitive impairment; NC, normal cognition; RAVLT, ray auditory verbal learning test.

Young aMCI mainly constituted of a low-risk group for AD, whereas the main group of old aMCI is at high risk for AD.

DISCUSSION

In this study, we compared CSF biomarkers in clinically diagnosed aMCI using samples from the ADNI database to compare the proportion of aMCI due to AD between young and old aMCI. As we postulated, much fewer patients with young aMCI compared with old aMCI had CSF signatures for AD.

Our results suggest that in young aMCI, careful interpretation of clinical diagnosis is required. In the present study, groups with different prevalence—young and old groups—were compared using CSF biomarkers. As predicted, the false-positive rate was higher in young aMCI than in old aMCI. When the patients with AD pathology were defined by a cutoff value of $A\beta_{1\text{-}42} < 192$ pg/mL, which is the most informative marker,[4,32] only 28.3% of patients with young aMCI had a substantial amyloid burden, whereas the prevalence was 63.2% of old aMCI. Other CSF biomarkers also showed a significantly higher rate of false positives in young aMCI. In addition, by using the values of CSF biomarkers and density plots of $A\beta_{1\text{-}42}$ concentration, we found that the distribution of results favored a non-AD etiology.

A similar situation exists with the conversion of aMCI to AD. The conversion rate of aMCI to AD reflects how many patients with aMCI due to AD are included in the group with clinically diagnosed aMCI. Usually, the conversion rate of aMCI to AD is higher in a referral center than that of aMCI in the community-based study.[1,33] This may reflect inherent biases associated with referral centers such as the exclusion of other causes of cognitive impairment. In addition, more serious cases with cognitive decline may be referred to these specialty centers. Consequently, the prevalence of aMCI due to AD identified by specialty clinics would be generally much higher than that of aMCI due to AD in the community. Our data suggests that differences in conversion rates may arise from differences in

prevalence between referral centers and community-based studies. However, it may be that individuals presenting for clinical evaluation may be more impaired than those in the community and hence at greater risk for progressive disease.[33]

The high rate of false positives in young aMCI is not related to the nature of the CSF biomarkers present in the young groups. The prevalence of CSF signatures for AD in patients with NC increased with increasing age. Therefore, the low presence of CSF signatures for AD in young aMCI may be related to age differences or admixture of other diseases common to this age group, such as frontotemporal degeneration.[34] In the present study, however, no significant differences in $A\beta_{1\text{-}42}$ and tau levels were observed in both young and old group of AD and NC. Therefore, apparent significance of abnormal CSF biomarkers indicates that AD was the same for both groups.

Interestingly, the presence of CSF signatures for AD was low in the oldest group of AD patients (aged 85 years and older). Only 53.8% of this group had $A\beta_{1\text{-}42} < 192$ pg/mL, although the presence of amyloid burden increases with age in the NC group. The t-tau and p-tau_{181} also show the same trend (Table S1, Supplemental Digital Content 1, http://links.lww.com/WAD/A95). There are 2 possible reasons for this. First, the diagnosis of dementia in the oldest old patient is more challenging. Visual/hearing loss and physical illness result in poorer performance on neuropsychological tests unrelated to actual cognitive ability.[35,36] Second, other pathologies such as Lewy body dementia, vascular pathologies, and age-related brain atrophy might contribute to these findings, leading to a greater prevalence of mixed pathologies. The number of the oldest old is rapidly increasing because of increasing longevity of the population[37]; therefore, the importance of studies on dementia in that group is also increasing. Further studies on AD without CSF signatures may be required.

There are a number of limitations to this study. First, CSF biomarkers are not gold standard in the diagnosis of AD, although they are a promising and important biomarker for AD.[5,8] Second, studies on the community-based population rather than a hospital-based study may be required because prevalence and PPV are specific to community-based studies. However, it is difficult to identify brain pathology in patients with aMCI or obtain samples for CSF biomarkers in the general population. Lastly, our findings might be altered if different cognitive cutoff points for aMCI or different types of memory tests, such as the more sensitive Ray auditory verbal learning test, were used.

Our study suggested the following important points regarding the diagnosis of aMCI attributable to AD in patients under the age of 65 years. First, the clinical criteria for aMCI should be cautiously applied in the younger population as the likelihood of non-AD pathology is significantly more likely in this group. Second, higher specificity of the clinical criteria for young aMCI may be required to obtain an adequate PPV. Third, clinical studies that include a large number of patients with young aMCI should be supported by analysis of biomarkers for AD. This requirement may be especially relevant when preventive medications become available. Lastly, when biomarkers are not available, the clinician should explain the need for longitudinal follow-up and possible further diagnostic tests to identify other non-AD pathologies.

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