APOE ϵ4 increases the risk of progression from amnestic mild cognitive impairment to Alzheimer's disease among ethnic Chinese in Taiwan

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ABSTRACT

Objective To evaluate the effect of the apolipoprotein E (APOE) ϵ4 in the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) in ethnic Chinese people in Taiwan.

Methods Subjects older than 60 years with normal cognition, MCI or AD were enrolled from the memory clinic from 2000 to 2008. Normal ageing and MCI subjects were evaluated with clinical and neuropsychological examinations annually, and their APOE genotypes were determined.

Results A total of 326 normal ageing subjects, 304 amnestic MCI and 537 AD patients were recruited at baseline. The frequencies of APOE ϵ4 were 22.1% in normal ageing, 26.6% in MCI and 40.8% in AD patients. During the follow-up period (42.5±18.5 months), there were 227 MCI patients, and 248 normal ageing subjects received one or more annual follow-up evaluation. The ϵ4 +carriers had a higher annual conversion rate than did the ϵ4-negative subjects either in the MCI (15.9% vs 9.0%) or in the normal ageing subjects (2.2% vs 0.7%). The mean survival time before progression to AD was 57.0 months for the MCI ϵ4+carriers, 85.9 months for MCI ϵ4-negative patients, 86.2 months for normal ageing e4+carriers and 120.8 months for normal ageing ϵ4-negative subjects. The adjusted hazard ratio of APOE ϵ4 for developing AD was 2.0 (95% CI 1.2 to 3.2) in MCI and 5.3 (95% CI 1.2 to 24.1) in normal ageing.

Conclusion APOE ϵ4 increased the risk of developing AD both in amnestic MCI and in normal ageing in a clinic-recruited ethnic Chinese population.

INTRODUCTION

Mild cognitive impairment (MCI) is considered a transitional stage between normal ageing and dementia. Some researchers regard amnestic MCI as very early Alzheimer's disease (AD). If amnestic MCI is a very early stage of AD, the same patho-aetiology, such as the higher frequency of the apolipoprotein E (APOE) ϵ4 allele in AD,[1 2] is expected in MCI. However, there is evidence that while MCI may progress to AD, progression to frontotemperal dementia, vascular dementia, dementia of the Lewy bodies or returning to normal cognition is also possible. Several studies have reported that APOE ϵ4 is an important predictor for the progression from MCI to AD in Caucasians.[3–7]

Our group previously reported the presence of APOE ϵ4 was less frequent in the Chinese population in Taiwan than in Caucasians.[2] It remains unknown about the prevalence of APOE ϵ4 in Chinese MCI subjects and if APOE ϵ4 possesses the same risk in the prediction of AD as Caucasians. Our previous study with a small sample size in MCI subjects shows that APOE ϵ4 was associated with smaller hippocampal volumes, although the frequency of APOE ϵ4 shows only a slight but insignificant increase in our MCI patients[8] The present study aimed to study the effect of APOE ϵ4 in ethnic Chinese MCI patients with a larger sample size and a longer follow-up period.

METHODS

Subjects

The subjects were recruited from the memory clinic of Taipei Veterans General Hospital in the period 2000–2008. Those who fit the diagnosis of AD, MCI or normal as regards cognition, those older than 60 years and those who agreed to longitudinal follow-up with clinical and neuropsychological examinations were included. The Institutional Review Board of Taipei Veterans General Hospital approved the study, and the participants and the main care givers of the AD patients provided informed consent.

Clinical and neuropsychological evaluations

All participants received a standard set of clinical and neuropsychological evaluations, which included: the Mini-Mental Screening Examination (MMSE),[9] nine-item verbal learning memory test,[10] modified Complex Figure Test (copy and 10 min recall),[11] categorical verbal fluency test (animal), 30-item Boston Naming Test,[12] modified Trail-Making B tests[13] and short-form Geriatric Depression Scale.[14] The Clinical Dementia Rating (CDR) scale[15] was used for the subjects suspected of suffering from dementia. Neurological examinations, laboratory tests and neuroimaging evaluation (brain computerised tomography or MRI) were performed to exclude underlying causes of dementia such as stroke, Parkinson's disease, thyroid dysfunction, renal insufficiency, unstable diabetes mellitus, vitamin B_{12} deficiency and neurosyphilis. APOE genotypes were analysed for all of the participants.

Diagnosis

The diagnosis of AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's and Related Disorders Association (NINCDS-ADRDA) for probable AD.[16] Amnestic MCI was diagnosed as having Petersen's criteria of

amnestic MCI,[17] as follows: (1) subjective memory complaints; (2) with objective memory impairment (scores of free delayed recall on a nine-item Chinese version verbal learning test were greater than one SD below the scores of age- and education-matched normal ageing subjects)[10]; (3) normal general cognitive function; and (4) with intact daily functioning. Subjects with MMSE scores lower than 24 or a definite clinical history of stroke were excluded. The normal ageing controls were recruited from volunteers, spouses of the AD or MCI patients and subjects who came to the neurological clinics for symptoms other than cognitive problems or neurodegenerative diseases. They also underwent all the same standard clinical and neuropsychological evaluations.

Annual follow-up evaluations

All of the participants received clinical and neuropsychological assessments annually. Whenever there was a decline in MMSE scores, more than one point's or two points' decrease in the verbal memory test or cognitive decline was reported by informants, the CDR scale was applied. When dementia was suspected, laboratory tests for screening possible underlying causes of dementia were conducted. The diagnoses of vascular dementia (VaD),[18] frontotemporal lobar degeneration (FTLD)[19] or dementia of Lewy bodies[20] were made according to their respective criteria.

APOE genotyping

APOE genotypes were determined using PCR amplification and restriction isotyping following methods described previously.[21] APOE genotypes were unknown to clinicians during the diagnostic process. For the purpose of analysis, APOE genotypes were dichotomised into either of ϵ4+carriers or ϵ4-negatives. Hardy–Weinberg equilibrium was determined by the χ^2 exact test.

Statistical analyses

Descriptive statistics were used to demonstrate the demographic and clinical characteristics of the three diagnostic groups of subjects. Baseline demographic data and scores of neuropsychological tests were compared using analysis of covariance (ANCOVA) controlling for age, sex and education with post-hoc Tukey adjustment. Carrier rates of APOE ϵ4 among groups were compared using the χ^2 test. The Kaplan–Meier survival-analysis method and Cox proportional hazard analyses, with AD as the event, were performed to study the effect of APOE ϵ4 in the rate of progression to dementia. In the hypothesis contrast, the null hypothesis was rejected with a type 1 or α error of <0.05. Data were analysed with SPSS release 16.0 for Windows (SPSS, Chicago, Illinois).

RESULTS

A total of 1167 subjects were recruited, including: 537 AD, 304 MCI and 326 normal ageing subjects. The baseline characteristics of the participants are summarised in table 1. The duration of follow-up ranged from 8 to 138 months (mean 42.5±18.5 months). The AD group was slightly older than the MCI group and normal ageing group (AD vs MCI vs normal: 77.2±6.4 years vs 75.3±5.6 years vs 73.1±6.0 years, F=48.451, p=0.001). There were no significant differences in educational levels between the normal ageing and MCI subjects, but lower education was noted in the AD group. The baseline prevalences of hypertension, DM, hyperlipidaemia, cardiovascular disease, smoking and alcohol consumption were the same among three study groups.

Table 1 Demographics of the study groups on age, gender, education and neuropsychological tests

Variables	Mild cognitive impairment	Alzheimer's disease	Normal
Age (years)	75.3 (5.6)* ‡	77.2 (6.4)†	73.1 (6.0)
Sex (male/female)	180/124	279/258	199/127
Education	11.1 (4.7)‡	8.2 (5.2)†	11.2 (4.0)
Mini-Mental State Examination	26.8 (1.8)* ‡	16.5 (6.3)†	28.5 (1.3)
Chinese version verbal learning test 10 min recall (nine items)	4.3 (2.2)* ‡	1.2 (1.9)†	7.4 (1.5)
Modified complex figure test copy	14.8 (2.5)	13.1 (3.2)†	15.2 (1.8)
Modified complex figure test 10 min recall	6.6 (3.7)* ‡	1.7 (2.4)†	9.9 (3.6)
Verbal fluency (animal)	13.6 (4.3)* ‡	9.8 (4.0)†	17.8 (5.4)
Modified trail making test-B test (s)	88.5 (33.1)‡	108.2 (25.1)†	59.4 (31.5)
Modified trail making test-B test (lines)	11.6 (3.7)* ‡	6.9 (4.9)†	13.3 (2.3)
Stroop test	24.7 (13.1)* ‡	14.5 (9.1)†	37.4 (12.0)

Significance of $p<0.05$ for analysis of covariance after controlling for age, gender, education and using the Tukey adjustment for multiple comparisons.
*Mild cognitive impairment compared with normal.
†Alzheimer's disease compared with normal.
‡Mild cognitive impairment compared with Alzheimer's disease.

Four hundred and seventy-five subjects, including 227 MCI patients and 248 normal ageing subjects, received one or more annual follow-up evaluations, following baseline assessment. The baseline demographics and neuropsychological performances for these 475 subjects are presented in table 2. Those who did not return for a follow-up evaluation were not significantly different from the subjects who underwent a longitudinal evaluation in the distribution of APOE genotype, sex and age.

APOE genotypes

The frequencies of APOE ϵ4 in three study groups are presented in table 3. The AD patients had a higher frequency of APOE ϵ4 than the MCI and normal ageing subjects. There were 35 (6.5%), 11 (3.6%) and three (0.9%) subjects with two ϵ4 alleles in the AD, MCI and normal ageing groups, respectively. Because the mean age was significantly different between the three diagnostic groups, we further compared the APOE ϵ4 frequency in different age groups. The differences in APOE ϵ4 frequency among the three groups were significant in the subjects younger than 90 years.

Table 2 Demographics and neuropsychological performance of the 475 normal or mild cognitive impairment subjects with at least once annual follow-up evaluation

Variables	Mild cognitive impairment N=238	Normal N=228
Age (years)	75.2 (5.3)*	74.1 (5.7)
Sex (male/female)	158/69	157/91
Education	11.2 (4.5)	11.3 (4.2)
Mini-Mental State Examination	26.7 (1.8)*	28.6 (1.3)
Chinese version Verbal learning test 10 min recall (nine items)	4.1 (2.2)	7.5 (1.5)
Modified complex figure test copy	14.9 (2.0)	15.6 (1.4)
Modified complex figure test 10 min recall	6.2 (3.6)*	9.9 (3.6)
Verbal fluency (animal)	13.5 (4.2)*	17.6 (5.4)
Modified trail making test-B test (s)	92.4 (32.2)*	58.8 (31.7)
Modified trail making test-B test (lines)	11.3 (3.8)*	13.6 (2.5)
Stroop test	25.1 (12.6)*	37.5 (12.1)

*Significance of $p<0.05$ for analysis of covariance after controlling for age, gender and education.

Table 3 Frequency of APOE ϵ4 in different age groups of the study subjects

	Frequency (%) of the apolipoprotein ϵ4 allele						
	Mild cognitive impairment patients		Alzheimer's disease patients		Normal		
Age group (years)	No ϵ4	ϵ4 carrier	No ϵ4	ϵ4 carrier	No ϵ4	ϵ4 carrier	p Value
60–69	39 (73.6)	14 (26.4)	43 (64.2)	24 (35.8)	84 (81.6)	19 (18.4)	0.039
70–79	142 (71.4)	57 (28.6)	165 (56.1)	129 (43.9)	141 (77.5)	41 (22.5)	<0.001
80–89	40 (81.6)	9 (18.4)	102 (61.4)	64 (38.6)	27 (69.2)	12 (30.8)	0.029
≥90	2 (66.7)	1 (33.3)	8 (80.0)	2 (20.0)	2 (100.0)	0 (0)	0.659
Total	223 (73.4)	81 (26.6)	318 (59.2)	219 (40.8)	254 (77.9)	72 (22.1)	<0.001

χ^2 was used for analysis.

Outcomes of the MCI patients and normal ageing controls

In the 227 MCI subjects, 70 (30.8%) progressed to AD, one (0.4%) progressed to dementia of Lewy bodies, one (0.4%) progressed to FTLD, and two (0.9%) progressed to VaD. Six of the MCI patients reverted to normal cognition. The subjects reverting to normal cognition had a higher mean score of Geriatric Depression Scale (5.4±4.6) than did the subjects remaining with MCI (3.9±3.0) or the subjects converting to AD (4.1±3.1), albeit the difference was not statistically significant. In the 248 normal ageing subjects, 19 (7.7%) progressed to MCI, 10 (4.0%) progressed to AD, and one (0.4%) progressed to VaD.

The annual conversion rate to AD is 10.8% per person-year for MCI and 1.1% per person-year for the normal ageing. The ϵ4+ carriers had a higher annual conversion rate than did the ϵ4-negative subjects either in the MCI patients (15.9% vs 9.0%) or in the normal ageing subjects (2.2% vs 0.7%).

Survival analysis for the effect of APOE ϵ4

The Kaplan–Meier analysis was conducted to assess the survival time before progression to AD in the normal ageing and MCI subjects. Initially, subjects were categorised according to the clinical diagnosis at baseline. The MCI patients had a higher risk and faster progression to AD than did the normal ageing subject. The mean survival time was 79.9 months (95% CI 69.3 to 90.6 months) for MCI and 118.2 months (95% CI 107.0 to 129.4 months) for normal ageing.

The normal and MCI groups were further categorised into ϵ4+carrier and e4-negative subgroups. The survival curves of four groups are presented in figure 1. Both ϵ4+carrier subgroups (ϵ4+ MCI and ϵ4+ normal subjects) exhibited a faster progression to AD than did the ϵ4-negative subgroups (logrank test comparing the four survival curves: p<0.001). The mean survival time before progression to AD was 57.0 months (95% CI 45.0 to 69.0 months) for the MCI ϵ4+carriers, 85.9 months (95% CI 73.9 to 98.0 months) for MCI ϵ4-negative patients, 86.2 months (95% CI 77.6 to 94.7 months) for normal ageing ϵ4 +carriers and 120.8 months (95% CI 109.3 to 132.3 months) normal ageing ϵ4-negative subjects.

The MCI ϵ4-negative subjects experienced poorer outcomes than the normal ϵ4+carriers. At the end of the third year, the cumulative survival ratio is 0.989 for the ϵ4-negative normal ageing subjects, 0.967 for the normal ageing e4+carriers, 0.714 for the ϵ4-negative MCI patients and 0.620 for the MCI ϵ4+carriers.

In the Cox survival regression analysis, age, MMSE scores at baseline evaluation, sex and years of formal education were all entered the regression model to control the possible confounding effects. The final Cox regression models are shown in table 4. The adjusted hazard ratio (HR) of progressing to AD with the APOE ϵ4+carriers was 2.0 (95% CI 1.2 to 3.3, p=0.008) for the MCI patients and 5.3 (95% CI 1.2 to 24.1, p=0.032) for the normal ageing subjects.

In addition to APOE ϵ4, age, lower baseline MMSE and fewer years of formal education also were risk factors for MCI to progress to AD (table 3). However, age was the only risk factor other than APOE ϵ4 to predict the development of AD in normal ageing.

DISCUSSION

The major concerns of persons who receive the diagnosis of MCI include whether they will progress to dementia, when they will progress to dementia and what are the determining factors. The main finding of this study is that APOE ϵ4 is an important risk factor for predicting AD both in amnestic MCI and in normal ageing subjects in the ethnic Chinese population in Taiwan.

Although APOE ϵ4 is an important predictor in the conversion of AD, the ϵ4-negative MCI patients still have a greater chance of having AD (an annual conversion rate of 9.0%) than the ϵ4 +positive normal ageing subjects (an annual conversion rate of 2.2%). This suggests that a subjective plus objective evidence of cognitive decline is a more powerful indicator for predicting the development of AD. However, APOE ϵ4 further increase the risk of AD in MCI subjects. When a 75-year-old man receives a diagnosis of amnestic MCI, there is a 10.8% chance that he will have AD in a year when his APOE genotype is unknown; however, the risk increases to 15.9% if he is an APOE ϵ4+ carrier.

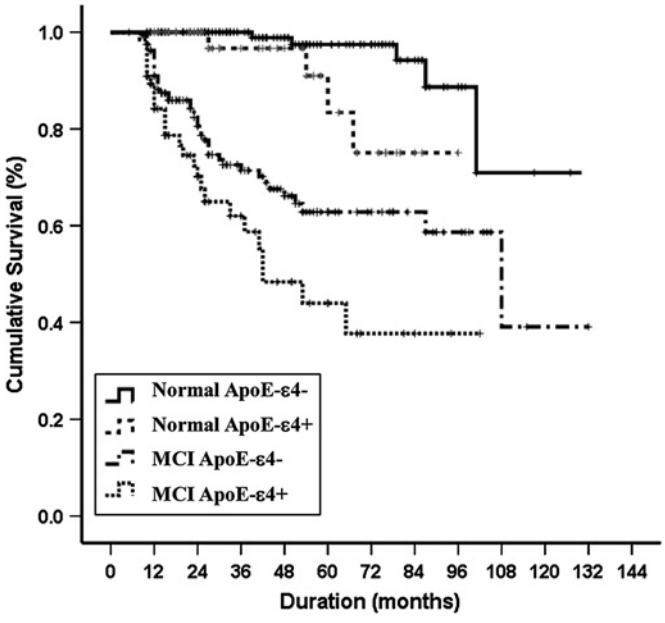

Figure 1 Kaplan–Meier analysis for the survival time of in normal ageing subjects and mild cognitive impairment (MCI) patients with or without apolipoprotein ϵ4 in developing Alzheimer's disease. The p value is <0.001 with the logrank test comparing the four progression curves. ApoE, apolipoprotein E.

Table 4 Cox regression models of the risk of apolipoprotein ϵ4 and other demographic data for the progression to Alzheimer's disease in mild cognitive impairment and normal ageing

	Mild cognitive impairment			Normal		
	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI	p Value
Age (years)	1.1	1.0 to 1.2	<0.001	1.2	1.0 to 1.3	0.044
Sex (female)	1.8	0.8 to 3.2	0.094	1.1	0.6 to 3.9	0.643
Education (years)	1.1	1.1 to 1.2	0.023	1.0	0.8 to 1.2	0.728
Mini-Mental State Examination	0.7	0.6 to 0.8	<0.001	0.9	0.6 to 1.7	0.905
Apolipoprotein ϵ4	2.0	1.2 to 3.3	0.008	5.3	1.2 to 24.1	0.032

Some researchers may question whether those who progressed to AD within 1 year actually already had AD. If they had been brought to the clinic just a few months later, they might have fitted all the diagnostic criteria for probable AD. There were 24 MCI subjects who progressed to AD in the first year, and 40.7% of them were APOE ϵ4+ carriers. This frequency is almost equal to the ϵ4+carrier frequency in our AD group. If amnestic MCI is actually a precursor of AD,[22 23] the frequency of APOE ϵ4 in amnestic MCI patients should be very similar to that of AD patients. However, the frequency of APOE ϵ4 in our MCI patients falls between that of the normal ageing subjects and the AD patients. Therefore, amnestic MCI may still be a heterogeneous group of patients with some in the very early stage of AD and some not having AD at all. The APOE ϵ4 frequency of those MCI subjects who did not progress to AD in 3 years (stable MCI) is lower than that of the early converters (24.1% vs 34.8%) and is almost equal to that of the normal ageing subjects (22.1%).

The prevalence of APOE ϵ4 of normal ageing controls in this study is similar to the frequency reported in our small sampled MCI study[8] but higher than our previous findings in a rural community.[21] This is a hospital-based study, and population characteristics in the present study may be not equivalent to those in communities. However, the incidence of dementia of our normal ageing group (1.1%/person-year) is in accordance with the rate noted in the community-based study in Taiwan (1.3%/person-year).[24] A further large community-based study to recruit subjects from different districts in Taiwan is needed to clarify the accurate prevalence of APOE ϵ4 in Taiwan.

The conversion rates of amnestic MCI to AD in previous studies vary from as low as 3.7%[25] to as high as 32%.[26] This discrepancy most likely resulted from the diagnostic and inclusion criteria for MCI varied widely among studies.[17 25 27 28] Whenever a higher degree of cognitive impairment is required in the inclusion criteria, higher conversion rates to dementia were noted.[27] We have made similar observations in our MCI studies in recent years. We added a criterion of CDR score=0.5 in the inclusion criteria of our previous study,[8] so the conversion rate from amnestic MCI to AD is higher (18%) than this study. In this study, we simply used Perterson's amnestic MCI criteria and excluded those subjects with an MMSE score lower than 24, so the conversion rate is lower than that of our previous study.

In a cross-ethnic and cross-cultural comparison study, Xu *et al* found that Chinese MCI subjects were 1.7 times less likely to progress to AD than were American subjects.[29] However, our MCI subjects had an annual conversion rate of 10.8%, which is similar to that in studies conducted for Caucasians. Recently another study by Xu *et al* also reported a 9.5% conversion rate from MCI to AD in China.[30]

Besides APOE ϵ4, age, lower baseline MMSE scores and less education were all risk factors for MCI progressing to AD. However, APOE is the most dominant factor for predicting the development of AD from normal ageing. Age was the only factor other than APOE ϵ4 that can predict AD in normal ageing subjects. The HR of APOE ϵ4 in normal ageing was even higher than that in MCI.

There were several limitations in the present study which should be addressed. First, the participants were recruited from a medical centre. The clinic-based study is prone to recruiting cases with a higher degree of severity or a longer period of illness. Therefore, the progression rate of the present study could be expected to be higher than community-based studies. However, our clinic-based study has an advantage in that its results will be more adaptable for clinical practice in memory clinics.

Second, the participants were evaluated every 12 months during the follow-up. The relatively long intervals may generate a time lag in establishing the survival time of onset of AD. Although CDR was rechecked whenever cognitive decline was reported or one point decline in MMSE was noted, MMSE has the shortcoming of insensitivity for detecting very mild cognitive decline.[31] Third, the follow-up duration might be insufficient to obtain a clearer final outcome of all the MCI patients. However, from a clinical point of view, determining the outcome in 3–5 years is far more practical and imperative.

In conclusion, the effect of APOE ϵ4 in predicting the progression to AD from amnestic MCI and normal ageing in ethnic Chinese population in Taiwan is comparable with that in Caucasians. APOE genotyping may help us further to identify subjects with high risk of AD.

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Competing interests None.

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