American Journal of Alzheimer's Disease & Other Dementias®
25(3) 233-238

DOI: 10.1177/1533317509357736
http://ajadd.sagepub.com
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Effects of Apolipoprotein E-ε4 and -ε2 in Amnestic Mild Cognitive Impairment and Dementia in Shanghai: SCOBHI-P

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Abstract

Objective: To determine apolipoprotein E (APOE)-ε4 and -ε2 frequencies and risk of mild cognitive impairment (MCI) and dementia in Shanghai, China. **Methods:** A total of 34 MCI and 34 dementia cases were recruited from an urban Memory Disorders Clinic and 32 controls were recruited from a residential community served by the clinic. Apolipoprotein E was genotyped using standard methods. **Results:** Among controls, frequencies were ε2, 0.11; ε3, 0.84; and ε4, 0.05; among MCI, 0.05, 0.77, and 0.18; and for dementia, 0.02, 0.84, and 0.15, respectively. In education-adjusted models, the odds ratio (OR) = 5.6 for dementia (95% CI = 1.09-29.3) and 4.7 for MCI (95% CI = 0.90-25.2) associated with any ε4 allele. The ε2 allele was inversely associated with dementia (OR = 0.12, 95% CI = 0.013-0.997) and MCI (OR = 0.38, 95% CI = 0.08-1.61). **Conclusions:** APOE-ε4 increases and -ε2 decreases the risk of dementia vs normal cognition. Similar trends were observed for amnestic mild cognitive impairment (aMCI).

Keywords

apolipoprotein E, dementia, mild cognitive impairment, China

Introduction

The apolipoprotein E (APOE)-ε4 allele is a strong risk factor for Alzheimer's disease (AD) among different ethnic groups[1-5] and age at onset is influenced by the number of APOE alleles.[6] Among African Americans, there is heterogeneity in risk of memory impairment from APOE, some showing similar effects as in Caucasians,[7] while others show no association.[2,8] The association between APOE-ε2 and AD is less clear, with some studies finding a clear inverse association[2,9,10] and others finding no association.[11]

The effect of APOE isoforms on the risk of dementia and mild cognitive impairment (MCI) in Chinese populations is of interest because the frequency of the risk allele for AD, APOE-ε4, is thought to be lower in China.[12] Therefore, the lower reported prevalence of dementia in China in some studies[3,13,14] may be in part explained by lower ε4 frequencies. The question of how the isoforms (ε2 and ε4) relate to dementia risk in non-Caucasians is important because it may point to a common pathogenesis across racial/ethnic groups.

Few studies have examined the associations between both APOE isoforms and MCI. It remains unclear at what stage ε4 and ε2 affect conversion: from normal cognition to MCI or from MCI to dementia/AD. If these effects are largely complete by the time a person meets criteria for MCI, then ε4 and ε2 would be acting early in the disease process to modify risk. It has been suggested that persons who are ε4 positive and develop AD show hypometabolism in temporal parietal regions while they are still asymptomatic.[15] Carriers of the ε4 allele can be distinguished by abnormal positron emission tomography (PET) scans in comparison with noncarriers when they are in their twenties.[16] If ε4 and perhaps ε2 have early effects, APOE

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may represent a viable target for preventing dementia. It is noteworthy that patients with MCI who are APOE-ε4 positive and who show increased amyloid burden on Pittsburgh compound-B positron emission tomography (PiB-PET) imaging have an increased rate of progression to AD.[17] This suggests that even if the role of APOE-ε4 begins early in life, it may nevertheless affect the rate of progression of the clinical expression of disease late in life.

In this study, we examined APOE allele frequencies in a sample of cognitively normal, community-dwelling elderly individuals and in cases with MCI and dementia in Shanghai, China.

Methods

Study Population

Subjects were participants in the Shanghai Community Brain Health Initiative-Pilot (SCOBHI-P), a case–control study of individuals living in Shanghai, China. The target sample included approximately equal numbers of participants with normal cognition (controls), MCI, and mild-to-moderate dementia living in the community. Cases of dementia and MCI were identified from the Memory Disorders Clinic (MDC) at Huashan Hospital, located in the Jing'an District of Shanghai. We identified these cases from incident cases that had first been seen at the MDC between May 2007 and November 2008. One hundred and nine cases and their informants were invited to participate; of these, 58 were recruited (53.2%). Of the 51 not recruited, 42 refused, 8 were unreachable, and 1 had a stroke. Potential controls were identified using a government-maintained "name list," which includes the name, sex, age, address, and telephone number of all residents. This list is kept current by the neighborhood administration office, which keeps track of all individuals living in that neighborhood, including in- and out-migration, as well as deaths. For this study, we obtained the name list for Jing'an and focused on a resident group in a defined geographic area, consisting of 5 buildings in the Jingansi Temple Community. Potential participants were approached at the door to describe the study. Of 71 potential participants from the name list, 10 refused (14%). An additional 3 names on the name list were unreachable. The recruitment rate in the community was 81.6%. When the 58 residents in the community were clinically evaluated, 2 met study criteria for dementia (3.5%) and 12 met Petersen criteria for MCI (20.6%). These 14 individuals were added to the case pool. Of the 116 cases and controls, we frequency matched a set of 32 normal controls, 34 MCI, and 34 dementia cases by age and sex for our analyses.

Of 34 participants who were diagnosed with MCI, 4 (12%) were found to have the nonamnestic type (naMCI), and 30 (88%) had the amnestic type (aMCI). We excluded naMCI cases from our analyses, because there was an insufficient number to analyze separately and we were interested in how dementia risk factors differed from aMCI, because aMCI progresses to dementia more commonly than naMCI.[18]

We obtained written informed consent from all cases and controls and their proxies. The study was approved by the Huashan Hospital, Fudan University in Shanghai, China, and the University of South Florida Institutional Review Boards.

Dementia and MCI Diagnoses

All individuals participated in a detailed physical and neurologic evaluation by study neurologists (QZ and QG), neuropsychological testing by trained, certified psychometrists, magnetic resonance imaging (MRI), blood donation, medical and family history, and other epidemiologic evaluations. The neuropsychological test battery consisted of the following instruments normed in Shanghai (by QG): modern Chinese Cognitive Abilities Screening Instrument (CASI),[19] WAIS-R Digit Span,[20] Bell Cancellation Test,[21] WMS Logical Memory Test[22] (immediate and delayed recall), Rey-Osterrieth Complex Figure[23] (copying and recall), Stroop Test,[24] Auditory Verbal Learning Test,[25] Category Verbal Fluency Test, WAIS-R Similarities Test,[20] Trail-Making Test,[26] Clock-Drawing Test,[27] Boston Naming Test,[28] and Mattis Dementia Rating Scale.[29] Consensus diagnostic conferences were conducted by the Chinese team (DD, QZ, QG, and ZH) with a subset of difficult cases also attended by members of the US team (RP, DG, DPS, ARB, and JAM). Dementia and its subtypes were diagnosed by criteria from the *Diagnostic and Statistical Manual* (Fourth Edition),[30] the National Institute of Neurological and Communicative Disorders and Related Disorders Association (NINCDS-ADRDA)[31] criteria for AD, and the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia.[32] Mild cognitive impairment and amnestic versus non-amnestic subtypes were applied from Petersen criteria[33,34] except that there was no requirement of a memory complaint from the participant corroborated by the informant. Objective memory impairment for age was based on norms developed by the neuropsychologist (QG) in Shanghai; we used the Chinese AVLT-long delay as evidence of memory impairment.[35,36] Preserved cognitive function in other domains was based on the neuropsychological battery. Largely intact activities of daily living was assessed by a 23-item instrument developed in Shanghai. All participants were administered detailed physical and neurologic examinations by study neurologists, and diagnoses were made for all participants and dementia criteria were ruled out for cases with MCI. Subtypes of MCI (amnestic MCI, single domain; amnestic MCI, multiple domain; non-amnestic MCI, single domain; non-amnestic subtype, multiple domain) were distinguished based on whether memory was impaired, in addition to language, attention, executive function, and visuospatial abilities on neuropsychological testing.

Qualitative assessment of whole brain atrophy and macrovascular lesions from each participant's MRI were used to assist in the diagnosis and subtyping of dementia.

Apolipoprotein E Genotyping

We obtained venous blood samples collected into EDTA anticoagulant from all cases and controls at Hua Shan Hospital. Lab technicians were blind to the diagnosis of the participants. Methods followed those of Emi[37] and Hixson.[38]

Other Covariates

An extensive risk factor questionnaire was administered to all proxies and all controls. Age was reported by proxies of cases and controls as was the highest level of education completed by the case and control. Educational level was coded as 0: no school; 1: primary school; 2: middle school; 3: high school; 4: college or university and 5: above university (postgraduate school). We collected the continuous number of years of education achieved, but 4 participants had missing data; therefore, educational level from the proxy interview was used instead.

Statistical Analyses

We used analysis of variance (ANOVA) to describe the differences between normal controls, aMCI, and patients with dementia for continuous variables, with Tukey multiple comparison procedure used for comparisons of individual means. For categorical variables, χ^2 was used to test for overall significance. Logistic regression models were built to predict the comparisons between dementia and controls and aMCI and controls for APOE genotypes. Dichotomous variables were created for "any ε4" and "any ε2" including ε2ε4 genotypes (included as "any ε4" in the ε4 analysis and "any ε2" in the ε2 analysis). Because the groups were well matched on age and sex, each model was run with APOE alone and then with education added to the model. All analyses were conducted using statistical analysis system (SAS) version 9,[39] with P values less than .05 (2-tailed) interpreted as being statistically significant.

Results

We compared the age and sex of the 64 participating cases with the 51 nonresponding cases. The mean age among the responding cases and their informants was 74.6 (SD = 5.0) and among nonresponding cases and their informants 75.6 (SD = 4.9; $t = 1.08$, $P > .20$). For sex, $\chi^2 = 0.47$, $P = .49$. Nonparticipants from the community were older (mean 76.1 [SD = 5.96] vs mean 73.4 [SD = 5.6]), but not significantly so ($P > .10$). Community-based nonparticipants also were more likely to be male (69.2% vs 51.6%), but this difference also was not statistically significant ($P = .28$).

Characteristics of the sample and the 3 groups are shown in Table 1. Mean age did not differ among groups ($F = .63$, $P = .54$). Matching on sex was achieved, with men and women comprising about half of each group ($P = .96$). Although educational attainment did not differ significantly between groups, 40% of aMCI had a college education or more compared with about 25% of the other 2 groups. The 3 diagnostic groups differed in mean Mattis Dementia Rating Scale score ($F = 54.4$; $P < .0001$). After adjustment for multiple comparisons (Tukey), all means were significantly different from one another.

Table 1. Descriptive Comparisons of Diagnostic Groups

	Controls (n = 32)	aMCI (n = 30)	Dementia (n = 34)
Mean age (SD)	73.4 (5.5)	74.8 (4.0)	74.4 (5.6)
Men (n and %)	16 (50.0)	15 (50.0)	18 (52.9)
Education (n and %)			
No or primary school	6 (18.8)	5 (16.7)	14 (41.2)
Middle school	7 (21.9)	3 (10.0)	5 (14.7)
High school	11 (34.4)	10 (33.3)	6 (17.6)
College or more	8 (25.0)	12 (40.0)	9 (26.4)
Mattis Dementia Rating Scale Score	134.7 (6.4)	123.2 (10.7)	103.0 (17.4)

Abbreviation: aMCI, amnestic mild cognitive impairment.

Table 2 shows the genotypes for the 3 groups. There were no ε2ε2 genotypes nor were any of the controls ε4ε4. Allele frequencies also are shown in Table 2.

Tables 3 and 4 show logistic regressions conducted to assess the risk of dementia and MCI from "any ε4" and "any ε2" allele, respectively. The adjusted odds ratio (OR) for dementia associated with ε4 was 5.6 (95% CI = 1.09-29.3), and for MCI, 4.7 (95% CI = 0.9-25.2). Corresponding models for ε2 were associated with inverse risk: for dementia, OR = 0.12 (95% CI = 0.01-0.997) and for MCI, OR = 0.37 (95% CI = 0.08-1.61). The ORs for MCI associated with both ε4 and ε2 were in the expected directions, although the power to detect a significant association was likely too low.

Discussion

The ε4 allele frequency among normal controls in our sample was 5%, considerably lower than in most Caucasian populations, where the frequency is 14%.[2,40] Despite the low frequency of ε4, this variant was strongly associated with dementia. The OR for dementia (5.6) was in the same range as most studies of Caucasians.[2] A very similar OR was found for the association between ε4 and MCI. However, due to limited power, it was not statistically significant. For ε2, we found the reverse trend: a statistically inverse association between ε2 and dementia and a trend for an inverse association with MCI. Again, the strengths of the ε2 association are in the same range as published studies.[2]

We found that frequencies of ε2 and ε4 were very similar in aMCI and dementia, and both differed substantially from the frequencies of these alleles in controls. Therefore, APOE appears to be having its effect relatively early in the disease process. If APOE genotype influenced AD pathology later, one would have seen a difference between dementia cases and aMCI. If the influence was gradual, one would expect all 3 groups to differ by APOE-ε4 frequency. The finding of similar frequencies between aMCI and dementia suggests that most of the effect may be evident by the time individuals are

Table 2. Frequencies of Apolipoprotein E (APOE) Genotypes and Alleles in Diagnostic Groups

	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4	Frequencies ε2	ε3	ε4	n
Controls	6 (18.75)	1 (3.13)	23 (71.88)	2 (6.3)	0 (0)	0.11	0.84	0.05	32
aMCI	1 (3.33)	2 (6.67)	20 (66.67)	5 (16.67)	2 (6.67)	0.05	0.77	0.18	30
Dementia	1 (2.94)	0 (0)	24 (70.59)	8 (23.53)	1 (2.94)	0.02	0.84	0.15	34
	8	3	67	15	3				

Abbreviation: aMCI, amnestic mild cognitive impairment.

Table 3. Logistic Regressions Comparing Dementia Cases to Controls and aMCI Cases to Controls for APOE-ε4, With and Without Adjustment for Educational Level

	Dementia (OR, 95% CI)		aMCI (OR, 95% CI)	
Model 1[a]	5.4	1.07-27.3	4.6	0.87-24.1
Model 2[b]	5.6	1.09-29.3	4.7	0.90-25.2

Abbreviations: APOE, Apolipoprotein E; aMCI, amnestic mild cognitive impairment.
[a] Crude.
[b] Adjusted (education was not significant in either model).

Table 4. Logistic Regressions Comparing Dementia Cases to Controls and aMCI Cases to Controls for APOE-ε2, With and Without Adjustment for Educational Level

	Dementia (OR, 95% CI)		aMCI (OR, 95% CI)	
Model 1[a]	0.11	0.01-0.94	0.40	0.09-1.71
Model 2[b]	0.12	0.01-0.997	0.37	0.08-1.61

Abbreviations: APOE, Apolipoprotein E; aMCI, amnestic mild cognitive impairment.
[a] Crude.
[b] Adjusted (education was not significant in either model).

diagnosable as aMCI. To evaluate this hypothesis further, a large, longitudinal study examining the evolution of aMCI to dementia and its subtypes would be necessary, in which one could also determine whether there is heterogeneity in the association between APOE and dementia versus APOE and AD.

Our estimate of the ε2 allele frequency is relatively high, even among Chinese studies, but agrees with those from Beijing[12] and Hifei.[41] More recent studies conducted among Caucasians show significant heterogeneity of ε2 frequencies, ranging from 1% to 15%.[42,43] The low frequency of ε2 from Finland has been noted[2,44] and may represent an outlier among Caucasian frequencies. Some studies of Caucasians[43,45,46] show ε2 frequencies close to our estimate of 11%.

The ε4 variant of APOE is a strong predictor of AD and is strongly related to its pathology.[5,47,48] Studies from China[3,4,49] and Taiwan[11,14,50] have replicated this finding and have also shown that in AD ε4 participants progress faster than non-ε4 participants.[51] A large study from Taiwan found higher mean cholesterol levels in ε4s and lower levels in ε2s, compared with ε3 homozygotes.[52] Some studies have found a clear protective effect of the ε2 allele.[2,9] In Sweden, this effect was limited to individuals younger than 85.[53] However, in Taiwan, ε2 was not associated with a reduced risk of AD.[11] In a recent study[54] of people dying in their 90s, ε2 carriers were not more likely to express dementia clinically but were 7.8 times more likely to meet neuropathologic criteria for AD compared with the ε3ε3 genotype (95% CI = 1.5-40.2). The protective effect of ε2 on dementia that we found is consistent with the relatively young mean age of our sample.

The mechanisms by which APOE genotypes lead to MCI and dementia remain controversial. It is known that APOE performs important functions in transporting cholesterol and phospholipids from astrocytes to neurons and that the absence of APOE results in dysfunction of terminal remodeling and synaptic replacement.[55] Individuals homozygous for ε2 express the highest level of APOE and those homozygous for ε4 the lowest. Apolipoprotein E-ε2 and -ε3 may have neuroprotective and neurotrophic roles in the normal aging brain and, therefore, it has been argued that individuals who do not possess an ε2 (or ε3) allele may be at risk of AD-type pathology.[47] Many studies have found that risk of AD increases with ε2 < ε3 < ε4[2,10,56-58] and that a gene dosage effect is evident with 0 ε4 < 1 ε4 < 2 ε4.[2,6]

Participants who carry the ε2ε4 genotype are sometimes excluded from analyses.[59] In a meta-analysis, individuals carrying this genotype were still at higher risk.[2] We categorized these individuals as possessing an ε4 allele and included them in the category of ≥1 ε4; we also included them in our ε2 analyses when considering ≥1 ε2. Exclusion of participants with the ε2ε4 in other analyses (not shown) had little effect on the ORs.

Only 2 studies have examined the role of ε4 on MCI in China and Taiwan.[41,60] In Hefei, China, a memory clinic–based and nursing home sample of 28 patients with MCI and 30 controls was recruited. Apolipoprotein E-ε4 was found to predict MCI status compared with controls. In Taiwan, an ongoing cohort study at Taipei Veterans General Hospital's neurology clinics was conducted from 1990 to 2003.[60] Fifty-eight participants with MCI were compared with 20 controls. The ε4 allele was present in a large proportion of the controls (20%) and, while 25.9% of the MCI participants possessed the ε4 allele, the difference was only marginally significant ($P = .06$). In our study, one or more ε4 alleles was present among 9.4% of our controls. Methodologic techniques used to select samples for study may explain these differences.

Strengths of our study include the detailed clinical work-ups done on all participants, including controls. In addition, controls in our study were recruited from the community served by the Memory Disorders clinic from which the cases were identified. In Shanghai, there is no medical referral system.

Individuals living in the community can seek care at any hospital in the city. Hua Shan Hospital, located in the community in which controls were recruited, is known in Shanghai for its Memory Disorders clinic. Therefore, individuals wishing to be seen by well-known neurologists come to the clinic and wait until they are seen the same morning. Therefore, there is less referral bias in this population than would be seen in a similar study conducted in the United States. This minimizes the referral bias in our study but may not eliminate it.

Limitations of our study include the relatively small size and cross-sectional nature of the study. This study was designed as a feasibility pilot study for a larger follow-on study. The percentage of dementia (3.5%) and cases with MCI (20.6%) found in the community of potential controls is likely illustrative of the frequency of MCI and dementia that is undiagnosed in the urban community in Shanghai.

Further research on the roles of the APOE-ε2 and -ε4 alleles require larger, prospective studies in China, in which specific genotypes can be examined in relation to incident dementia and MCI risk. However, our study demonstrates that the pathogenesis of dementia and aMCI is similar in Chinese and Caucasians with regard to the role that APOE plays.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

NIH R21 AG028182

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