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Association between *APOE* ε4 Allele and Vascular Dementia: The Cache County Study

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Key Words
APOE · Vascular dementia

Abstract
Background: The *APOE* ε4 allele is an established risk factor for Alzheimer's disease, but reports of its association with vascular dementia (VaD) have been inconsistent. We examined the relationship between *APOE* ε4 allele and the risk of incident VaD in a large, population-based cohort of elderly adults with up to 10 years of follow-up between 1995 and 2005. ***Methods:*** A total of 3,424 elderly men and women free of dementia were genotyped at the baseline assessment. Incident VaD was identified through standardized procedures administered at 3 follow-up assessments. Cox proportional hazards models were used to evaluate the risk of VaD associated with *APOE* ε4. ***Results:*** The adjusted hazard ratio was 1.6 for the participants with 1 *APOE* ε4 allele (95% CI: 0.9–2.7; p = 0.083) and 4.4 for those with 2 *APOE* ε4 alleles (95% CI: 1.6–12.5; p = 0.005). The increased risk did not appear to be mediated by vascular risk factors. ***Conclusions:*** The *APOE* ε4 allele is associated with an increased risk of VaD in a dose-dependent fashion and accounts for almost 20% of VaD in the population.

Introduction

Vascular dementia (VaD) is one of the most common forms of dementia, second only to Alzheimer's disease (AD). In 2002, the estimated prevalence of VaD among individuals aged 71 years and older in the USA was 2.4%, compared to 9.7% for AD [1]. Similar to AD, the public health burden of VaD threatens to worsen considerably as the world's population ages [2].

Variation at the apolipoprotein E *(APOE)* gene is a well-established risk factor for late-onset familial and sporadic AD [3, 4]. The gene is on chromosome 19 and encodes a major apolipoprotein which serves as a cholesterol carrier in the brain [5]. It has 3 common alleles (ε2, ε3 and ε4), which determine 6 different genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4). The ε4 allele is associated with a greater risk of AD in a dose-dependent fashion, while some evidence suggests the ε2 allele is associated with a lower risk [6].

The *APOE* gene has also been associated with VaD in different ethnic groups [7–12], but this association has not been consistently replicated [13–17]. All prior studies of this topic have used case-control or cross-sectional study designs, and many have also had relatively small

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sample sizes and relatively weak control on population stratification by age, gender, ethnicity or other unknown confounding factors. An especially problematic issue in this area of research is the diagnostic misclassification of mixed dementia as VaD.

We investigated the association between *APOE* and incidence of VaD in the Cache County Study cohort, a large and well-characterized, population-based sample of 5,092 older adults who have had up to 10 years of longitudinal follow-up since 1995.

Methods

Overview

The Cache County Study is a prospective study of the prevalence and incidence of dementia in relation to genetic and environmental risk factors among elderly adults living in Cache County, Utah, USA. The study design has been reported in detail previously [18, 19]. Briefly, all residents of the county aged 65 years or older on January 1, 1995, were invited to participate, and 5,092 (90%) completed baseline assessments and interviews in 1995–1996 (wave I). Surviving participants who had not met criteria for the diagnosis of any dementia were then asked to engage in follow-up evaluations in 1998–1999 (wave II), 2002–2003 (wave III) and 2005–2006 (wave IV). At each evaluation, a multistage screening and assessment procedure was used to determine the cognitive status of the participants, and the presence and type of dementia. In addition, detailed interviews were used to gather information on the participants' demographics, family and medical history. All protocols were approved by the Institutional Review Boards of Utah State University, Duke University and Johns Hopkins University. Spouses or next of kin gave informed consent when participants were unable to provide it.

Study Sample

The present study used data collected from wave I to wave IV. A total of 5,092 elderly individuals from Cache County participated in wave I of the study. At baseline, we identified 359 cases of dementia; these individuals were excluded from the current analyses. By the end of wave II, 633 persons had died and another 676 persons were lost to follow-up. Thus, 3,424 individuals had completed at least 1 follow-up and were available for inclusion in the current study.

Diagnosis of VaD

A similar assessment procedure was utilized at each wave of the study. Participants were initially screened by questionnaires sensitive to detecting dementia, including a revised version [20] of the modified Mini-Mental State Examination (3MS) [21]. We interviewed knowledgeable collateral informants of those who were unable to complete the 3MS using the Informant Questionnaire for Cognitive Decline in the Elderly [22]. In waves I and II, participants with low screening scores were further evaluated using the Dementia Questionnaire [23] administered by phone to a collateral informant. In these waves, all participants aged 90 years or older, regardless of their scores on the 3MS or Informant Questionnaire for Cognitive Decline in the Elderly, were also evaluated using the Dementia Questionnaire.

Based on the results of the initial screening, participants with evidence of cognitive impairment were referred for a detailed structured clinical assessment conducted by research nurses and psychometricians in the presence of a collateral informant. A systematic random subsample of participants comprising approximately 19% of the cohort, as well as all participants over the age of 85 years in waves III and IV, were also sent for a clinical assessment regardless of their scores on the screening evaluations. The assessments included: a clinical and medical history, family history of dementia, a brief physical examination, a standardized blood pressure measurement, a structured neurologic examination, the Neuropsychiatric Inventory [24], an assessment of cognitive and functional impairment using the Dementia Severity Rating Scale [25], and a 1-hour battery of neuropsychological tests [26].

Board-certified geriatric psychiatrists and neuropsychologists then reviewed the results of the clinical assessments and assigned working diagnoses of dementia, based on the DSM-III-R criteria [27], or other cognitive syndromes. The estimated age at onset of dementia was recorded as the year in which participants unambiguously met the DSM-III-R criteria. Participants with working diagnoses of dementia or other cognitive disorders were reexamined by a study physician and asked to undergo standard laboratory tests and a brain MRI for differential diagnosis. Finally, a panel of expert clinicians reviewed all available information and adjudicated a final differential diagnosis of dementia using NINCDS-ADRDA criteria [28] for AD, NINDS-AIREN criteria [29] as modified by Tatemichi et al. [30] for VaD and current research criteria for other dementing illnesses. For present purposes, we restricted the diagnosis of VaD to participants whose dementia was believed to be exclusively cerebrovascular in origin, having no features that were specifically suggestive of AD or other dementias. The sensitivity and specificity of the above screening methods for the detection of incident dementia have been estimated at 84.7 and 95.2%, respectively [31].

APOE *Genotyping*

Buccal DNA samples were obtained at the baseline assessment with a response rate of 97%. *APOE* genotypes were determined using PCR amplification and a restriction isotyping following the methods described previously [32, 33]. The *APOE* genotypes were not known to clinicians during the diagnostic process.

Vascular Risk Factors

Medical histories of vascular risk factors were obtained at the baseline and follow-up visits via proxy- and self-report. The participants were asked about a number of vascular factors and their history of cardiovascular events including hypertension, hypercholesterolemia, diabetes mellitus, stroke, coronary artery bypass graft (CABG) and myocardial infarction (MI). A positive history of each condition was recorded when the participant, or proxy informant, indicated he/she was ever told by a doctor or nurse that he/she had the condition or received treatment for it.

Statistical Analysis

Demographic comparisons evaluated potential differences in age, sex, education, *APOE* genotype and history of vascular risk factors at baseline between individuals diagnosed with VaD and those who were censored. Continuous variables were examined

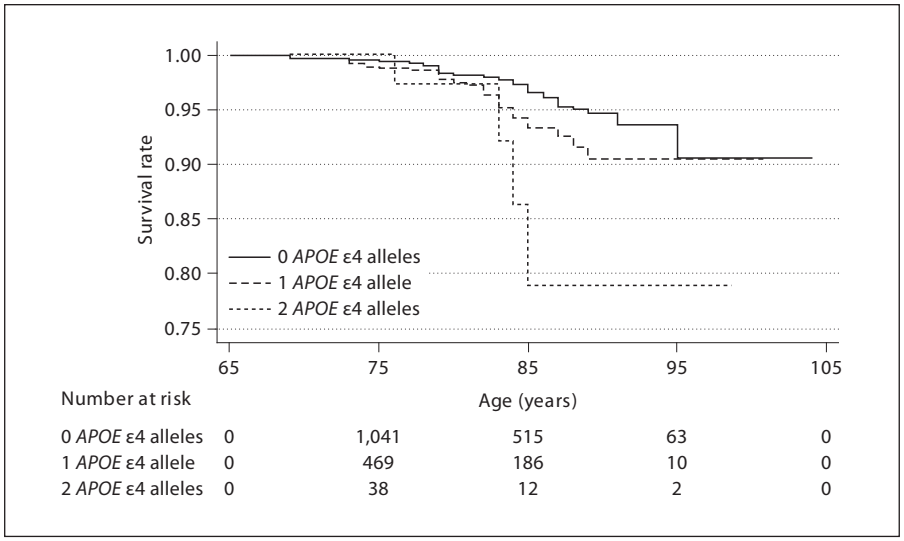

Fig. 1. Kaplan-Meier survival curves for participants with 0, 1 and 2 *APOE* ε4 alleles. Survival rate calculated by S(t) = probability survival > t, where t = age.

using t tests or analyses of variance, while categorical variables were examined via χ^2 tests.

The Kaplan-Meier survival analysis and log rank test were used to evaluate the differences of VaD-free survival in groups with 0, 1 or 2 *APOE* ε4 alleles. Age was used as the time scale, with age at baseline as the origin. Participants who developed VaD were captured as having an event at the estimated age of dementia onset. Participants who survived without dementia, died or were lost to follow-up were censored at the age of their last wave of assessment, while participants who developed other forms of dementia were censored at their estimated age of dementia onset. Cox proportional hazard models were then used to assess the association between the number of *APOE* ε4 alleles and the risk of VaD, controlling for age at baseline, gender, years of education and vascular risk factors. The results were presented as hazard ratios (HR) with 95% confidence intervals (CI). Finally, the population attributable fraction (PAF) of VaD due to the *APOE* ε4 polymorphism was calculated. The PAF is an estimate of the proportion of a population's burden of disease that could be prevented if the effects of specific causal factors were eliminated from the population. It was calculated as follows: P × (multiple adjusted HR – 1)/multiple adjusted HR, where P = proportion of cases exposed to any *APOE* ε4 alleles [34]. All analyses were performed using STATA version 10 software (StataCorp, College Station, Tex., USA). Two-sided $p < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics by diagnosis of VaD during follow-up from wave II to wave IV of the Cache County Study (n = 3,424)

	Non-VaD[1] (n (%) = 3,359)	VaD (n (%) = 65)	p
Male, n (%)	1,404 (41.8)	30 (46.2)	0.48
Age, mean years ± SD	74.5 ± 6.47	76.6 ± 6.49	0.01
Education, mean years ± SD	13.4 ± 2.87	13.3 ± 2.99	0.79
Number of ε4 alleles[2], n (%)			0.042
0	2,297 (69.0)	37 (56.9)	
1	950 (28.5)	24 (36.9)	
2	82 (2.5)	4 (6.2)	
Prevalence of vascular risk factors[2], n (%)			
Hypertension	1,467 (43.8)	40 (62.5)	0.003
High cholesterol	1,084 (32.6)	20 (36.7)	0.892
Diabetes mellitus	371 (11.1)	19 (29.2)	<0.001
Stroke	133 (3.9)	17 (26.2)	<0.001
CABG	216 (6.4)	6 (9.2)	0.365
MI	365 (10.9)	15 (23.1)	0.002

[1] Included are diagnoses of dementia other than VaD.
[2] This is the percentage out of the total number with nonmissing data.

Results

Out of the 3,424 participants who completed the baseline evaluation and at least 1 follow-up, there were 65 cases of incident VaD over a mean follow-up period of 7.1 years (range: 0.02–12.4 years; standard deviation = 3.5 years). A total of 1,309 participants (from the original 5,092) were lost to follow-up. These individuals tended to be older (t = 19.7; $p < 0.0001$) and less educated (t = –7.04; $p < 0.0001$), and more of them were male ($\chi^2 = 6.05$; p = 0.014). The distribution of *APOE* ε4 alleles was similar in those who were lost versus those who were not. Table 1

Table 2. HR for risk of incident VaD by Cox's proportional hazards models

	Crude HR	Model 1 aHR	Model 2 aHR
0 *APOE* ε4 alleles	1.0 (ref)	1.0 (ref)	1.0 (ref)
1 *APOE* ε4 allele	1.69 (1.00–2.83)	1.70 (1.01–2.84)	1.60 (0.94–2.71)
2 *APOE* ε4 alleles	4.00 (1.42–11.2)	3.98 (1.41–11.2)	4.44 (1.55–12.5)
Age at baseline[1]		1.00 (0.92–1.08)	0.95 (0.88–1.04)
Sex		0.78 (0.47–1.28)	0.86 (0.50–1.46)
Education in years		0.98 (0.90–1.07)	0.95 (0.88–1.04)
Hypertension			1.64 (0.96–2.81)
High cholesterol			0.77 (0.43–1.35)
Diabetes			2.83 (1.59–5.07)
Stroke			6.27 (3.40–11.5)
CABG			0.87 (0.32–2.32)
MI			1.76 (0.89–3.49)

Values in parentheses denote 95% CI unless stated otherwise. aHR = Adjusted HR.
[1] Age while on study was used as the time axis in the Cox proportional hazards models, and age at baseline was further added to the models to provide additional control for any possible cohort effects.

presents the demographic characteristics of the sample included in this analysis. Compared with the non-VaD group, individuals with incident VaD were significantly older, were more likely to have 1 or more *APOE* ε4 alleles, and more often reported at baseline that they suffered from hypertension, diabetes, stroke or MI. There were no material differences in gender distribution and years of education between these 2 groups.

The Kaplan-Meier curves for VaD-free survival for participants with 0, 1 and 2 *APOE* ε4 alleles are displayed in figure 1. Participants with 1 or 2 *APOE* ε4 alleles had significantly lower VaD-free survival rates than the reference group with no *APOE* ε4 alleles (log rank test: p = 0.044 and 0.0038, respectively). The Cox proportional hazard models also showed that those with 1 or 2 *APOE* ε4 alleles had a greater risk of developing VaD in a dose-dependent fashion (table 2). Importantly, this association persisted even after adjustment for cardio- and cerebrovascular factors including history of hypertension, diabetes, high cholesterol, stroke, MI and CABG, suggesting the association was not mediated by these factors. Finally, we grouped together participants with 1 or 2 *APOE* ε4 alleles and compared them to those without any ε4 alleles, obtaining an adjusted HR of 1.85 (95% CI: 1.13–3.03; p = 0.015). Given the effect size and frequency of the ε4 alleles, the proportion of population risk attributable to any *APOE* ε4 allele (PAF) for VaD was estimated to be 19.8%.

Discussion

In this large, prospective cohort study, there was a dose-dependent association between the presence of 1 or 2 *APOE* ε4 alleles and the risk of VaD. Compared to individuals without any *APOE* ε4 alleles, those with 1 *APOE* ε4 allele had an approximately 1.7-fold greater risk of VaD, whereas those with 2 *APOE* ε4 alleles had a 4-fold greater risk. The population attributable risk associated with having 1 or more *APOE* ε4 alleles for VaD was 19.8%.

There has been a matter of controversy about the association between *APOE* ε4 allele and the risk of VaD in the literature. Some studies reported positive associations [7–12], while others showed no associations [13–17]. Even regarding the same ethnic groups, the results have been in conflict [9, 15]. There are several potential reasons for the inconsistent findings. First, all previous studies have used a cross-sectional or case-control study design, both of which are more susceptible to selection bias. Second, the small sample sizes of some studies may have offered inadequate statistical power to detect an association. Lastly, the diagnosis of VaD using the NINDS-AIREN can be challenging, and outcome misclassification may therefore have led to divergent results [35].

VaD, by name, implies a link between vascular risk factors or vascular diseases and dementia syndromes. Vascular risk factors such as hypertension, diabetes, hypercholesterolemia and smoking have been implicated as risk factors for dementia as have vascular diseases (for a

review see Luchsinger and Mayeux [36]). On the other hand, the earliest research on the expression of the *APOE* genotype focused on its influence on lipid metabolism and atherogenesis [37]. Therefore, it has been postulated that an effect of *APOE* on dementia may be mediated by dyslipidemia and vascular diseases [38, 39]. If so, the association between *APOE* and dementia might be expected to attenuate after adjusting for vascular risk factors and diseases. In our analysis, we observed no attenuation of the association between *APOE* ε4 allele and the risk of VaD after adjusting for vascular risk factors. Thus, it appears the effect of the *APOE* ε4 allele on the risk of VaD is not mediated by vascular factors. This finding is consistent with one previous study [40].

Advantages of the current study are its large, population-based cohort with up to 10 years of longitudinal follow-up. Also, the diagnosis of VaD followed a structured, multistage diagnostic procedure, supported by laboratory and neuroimaging studies and adjudicated by a panel of experts. Furthermore, we considered as cases only subjects who had a diagnosis of pure VaD without any clinical evidence of an AD contribution. This approach would make the diagnostic entity of VaD more homogeneous although the possibility of diagnostic misclassification cannot be totally ruled out because of the lack of neuropathological confirmation. A limitation of the study is its lacking generalizability. Over 95% of this population is Caucasian, and there may be differences in the genotype distribution and genetic mechanism in other ethnic populations. On the other hand, the relatively homogeneous population makes it less likely that the association we observed was due to population confounds.

In summary, our findings suggest that the *APOE* ε4 allele confers a significant risk for VaD, and this effect did not seem to be mediated by vascular risk factors and diseases. Other possible mechanisms of how the *APOE* ε4 allele increases the risk of VaD should be explored in future studies.

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