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Is ApoE ε4 Associated with Cognitive Functioning in African Americans Diagnosed with Alzheimer Disease? An Exploratory Study

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Abstract

Objective—The effect of the apolipoprotein ε4 allele (ApoE ε4) on cognitive performance in patients with probable Alzheimer disease (AD) has been studied in primarily Caucasian samples. The aim of this exploratory study was to examine whether the presence of ApoE ε4 is associated with cognitive performance in African American AD patients.

Methods—A cross-sectional, retrospective design was used to address the study objective. Data were extracted from the records of 65 African American patients who participated in the National Institutes of Health-National Institute on Aging (NIH-NIA) Emory University Alzheimer Disease Center Registry. Inclusion criteria were a clinical diagnosis of probable AD, cognitive testing using the Mattis Dementia Rating Scale and the Consortium to Establish a Registry for Alzheimer Disease (CERAD) neuropsychological battery, and ApoE genotyping.

Results—Seventy percent of the patients were ApoE ε4 positive. Multiple regression analyses indicated that ApoE ε4 was significantly associated with poorer design copying (CERAD Constructional Praxis subtest), but other significant relationships were not observed between positive ε4 status and cognitive performance.

Conclusions—These preliminary findings suggest that the ApoE ε4 allele is not strongly associated with a particular pattern of cognitive functioning in African Americans once they are diagnosed with AD. However, these findings require replication in a large prospectively recruited and population-based sample of African American AD patients before firm conclusions can be reached.

Keywords

African Americans; ApoE ε4 allele; dementia; neuropsychological testing

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Apolipoprotein E (ApoE) ε4 increases the risk of both age-related cognitive decline and the transition from mild cognitive impairment to Alzheimer disease (AD).[1,2] Moreover, there is evidence that AD patients who are ε4 carriers have a faster rate of cognitive decline,[3,4] although negative findings exist as well.[5,6] In contrast to these investigations, there is relatively little known about whether ApoE ε4 affects the cognitive presentation of AD. A few studies have investigated this issue and have reported that ε4 carriers exhibit a phenotype characterized by greater memory impairment. It has been found that AD patients who have memory complaints as their presenting problem are significantly more likely to be ε4 carriers.[7,8] In addition, greater memory deficits on formal neuropsychological testing have been observed in AD patients who are ε4 carriers.[9] Marra et al[10] reported that the relationship between positive ε4 status and poor memory function was confined to patients who had an early disease onset (<65 years old) versus a late onset (>80 years).

These studies on ApoE ε4 status and the cognitive features of AD patients have involved predominantly Caucasian samples. An exception is a study by Fillenbaum et al[11] that compared the effects of ε4 status on baseline cognitive functioning in African American versus Caucasian AD patients. Although cognitive functioning was poorer in ε4 carriers, this effect did not significantly differ as a function of race.

The purpose of our exploratory study was to examine the association between ε4 status and neurocognitive functioning in African American AD patients. Research indicates that the AD incidence is greater for African Americans compared to Caucasians.[12,13] Therefore, it is important to determine whether there is a particular cognitive phenotype in African American ε4 carriers that might assist with the detection and implementation of pharmacologic treatment. In contrast to the investigation by Fillenbaum et al,[11] which administered a global measure of cognitive functioning known as the Short Portable Mental Status Questionnaire, we evaluated specific domains including language, verbal and visual memory, and visuoconstructive skills. We tested the primary hypothesis that ApoE ε4 positive individuals would demonstrate lower neuropsychological test performance, especially involving memory, compared to AD participants without ApoE ε4, after adjusting for possible confounders including demographic and clinical features.

Methods

Participants

The sample consisted of 65 African American patients with probable AD who participated in the NIH-NIA funded Emory Alzheimer Disease Research Center. All participants were non-institutionalized and living in a major metropolitan city in the Southeastern part of the United States. The participants' ages ranged from 58 to 95 years with a mean age of 77.1 (SD = 6.9); the educational attainment ranged from 2–18 years with a mean level of 9.4 (SD = 4.0). The Mini-Mental State Examination (MMSE)[14] score averaged 15.1 points (SD = 5.1, Range = 5–25). Informed consent was obtained from each participant and from a caregiver by protocols approved by the Emory University Institutional Review Board.

ApoE Genotyping

ApoE genotyping was performed on blood samples using PCR followed by digestion of the PCR product with Hha-I and visualization of the resulting bands by polyacrylamide gel electrophoresis.[15] Clinicians were unaware of the genotype results when the diagnosis of probable AD was given and when the neuropsychological exam was performed. Moreover, genotyping was performed without knowledge of the clinical diagnosis.

Clinical Assessment

Neurologists and neuropsychologists who have expertise in dementia examined the patients enrolled in the study. Each patient satisfied diagnostic criteria set forth by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD.[16] Trained assistants administered neuropsychological tests to patients to evaluate their level of cognitive functioning.

Cognitive Measures

The battery of neurocognitive tests included the Mattis Dementia Rating Scale (DRS) and the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological assessment battery. The DRS[17] is a measure of global cognitive functioning, and Shay et al[18] found that the DRS provides a clinically valid measure of stage of impairment with good reliability. DRS subtests include measures of attention (eg digit span), initiation and perseveration (eg performing alternating hand movements), construction (eg copying designs), conceptualization (eg similarities), and verbal and non-verbal short-term memory (eg sentence recall and design recognition). The maximum total score is 144, with lower total and subtest scores reflecting greater impairment.

The CERAD battery[19] was constructed to assess multiple areas of cognitive functioning (eg memory, language, and praxis) affected in AD.[20] It has high interrater and retest reliability in AD patients. The following neuropsychological tests are included in the CERAD battery. The verbal fluency (animal category) test measures verbal production, semantic memory, and language. The patient has 60 seconds to generate the names of as many animals as possible. The score is the total number of different animals named. The Boston Naming Test-CERAD modified items measure visual naming of 15 objects presented as line drawings. The items are arranged from easy to difficult. The maximum possible score is 15 correct responses. The word list learning measure assesses the ability to immediately recall as many words from a list of 10 words that are read out loud by the examiner. Three learning trials are administered, and the maximum number of correct responses is 30 words for the 3 trials. The delayed word list recall task assesses the ability to recall the 10 words from the immediate word list memory task after about a 5-minute delay. The amount of information saved from the third learning trial to the delayed recall trial is recorded. The constructional praxis test measures visuomotor abilities by having patients copy designs that increase in complexity.

Statistical Analyses

We examined the relationship between ApoE ε4 and cognitive functioning in the patients by fitting multiple linear regression models with ApoE ε4 status (yes/no) included as an explanatory variable. To adjust for possible confounding, we included current age, years of education, and vascular comorbidity defined as a history of hypertension, diabetes, and cardiac disease as explanatory variables in the model.

Results

One-way analyses of variance revealed no significant differences ($P > 0.05$) between ApoE ε4 carriers and non-carriers in age (ε4 positive: mean 76.1, SD 7.2; ε4 negative: mean 79.5, SD 5.6), education (ε4 positive: mean 9.8, SD 4.1; ε4 negative: mean 8.4, SD 3.8), and MMSE[14] scores (ε4 positive: mean 14.6, SD 5.2; ε4 negative: mean 16.2, SD 4.5). A greater proportion of the ε4 noncarriers (95%) had vascular comorbidities compared to ε4 carriers (72%), Fisher exact $P = 0.04$.

Table 1 shows the unadjusted mean scores of the groups on the Mattis DRS and the CERAD neuropsychological assessment battery. Table 2 presents the results of the multiple regression analyses predicting cognitive performance as a function of ApoE ε4 status while adjusting for age, education, and vascular comorbidities. The overall regression was significant for the CERAD constructional praxis subtest, with the presence of ApoE ε4 associated with poorer performance. However, no other significant effects of ε4 status were observed on other measures. Higher education was associated with significantly better performance on the DRS conceptualization scale, and the CERAD constructional praxis and immediate word recall subtests. Finally, the presence of vascular comorbidity was significantly associated with better naming performance.

Of the 35 patients who were ApoE ε4 carriers, 25 were heterozygous and 10 were homozygous. Regression analyses were re-run with the number of ε4 alleles (0, 1, or 2) as a predictor of cognitive performance. The results indicated that an increase in the number of ε4 alleles was significantly associated with poorer performance on the CERAD constructional praxis subtest (coefficient −0.21, SE 0.44), $P < 0.01$). No other significant relationships with ApoE ε4 were observed for the other cognitive domains.

Discussion

Based upon prior studies,[7–10] it was expected that memory performance would be significantly poorer in African American AD patients who are ε4 carriers. This hypothesis was not borne out. Of all the cognitive abilities measured, only visuomotor performance (CERAD constructional praxis) was found to be significantly worse in ε4 carriers versus noncarriers. There was also an expected dose-response relationship with poorer constructional abilities and an increase in the number of alleles (0–2). Other cognitive domains, however, were not associated with the genetic risk for AD.

It is important to emphasize that our investigation is exploratory. Our sample size was extremely small, and our patients came from memory assessment clinics as opposed to being

randomly recruited from the community. Moreover, a comparison of our findings with what has been found in Caucasian samples is overly simplistic, because it ignores other factors, apart from genetics, that can create apparent disparities. For example, differential item functioning, such as cultural differences in familiarity with wording of certain test items may play a role in these largely negative results compared to the positive findings in Caucasian AD patients.

Conclusion

These preliminary results do not provide support for a relationship between the presence of the ApoE ε4 allele and the pattern of cognitive functioning in African Americans once AD is diagnosed. Future research on a large epidemiological sample, with "deconstruction" of the concept of race,[21] is necessary to adequately address possible genetic contributions to cognitive performance in African Americans.

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Key Points

- The incidence of Alzheimer disease (AD) is significantly greater in African Americans compared to Caucasians.
- The aim of this exploratory study was to examine whether the presence of ApoE ε4 is associated with cognitive performance in African American AD patients.
- The effects of ApoE ε4 on cognitive performance in probable AD have been studied in primarily Cauca-sian patients.
- Our preliminary findings suggest that the ApoE ε4 allele is not strongly associated with a particular pattern of cognitive functioning in African Americans once they are diagnosed with AD.

Table 1

Unadjusted mean performance on the Mattis Dementia Rating Scale and the CERAD Neuropsychological Assessment Battery as a function of ApoE ε4 status[a]

	ApoE ε4 positive		ApoE ε4 negative		
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	***P***
Mattis Dementia Rating Scale (maximum possible points)					
Total score (144)	97.1 (17.2)	55–122	94.3 (17.6)	64–123	0.57
Attention (37)	31.6 (3.6)	22–37	31.6 (4.4)	22–37	0.98
Initiation/perseveration (37)	24.4 (7.4)	8–36	22.1 (6.7)	10–34	0.25
Construction (6)	3.7 (1.6)	1–6	4.1 (1.6)	2–6	0.47
Memory (25)	10.8 (3.2)	3–21	10.8 (3.3)	5–18	0.99
Conceptualization (39)	26.5 (7.3)	5–37	24.8 (6.2)	15–34	0.39
CERAD					
Animal fluency (no limit)	8.3 (3.0)	4–16	7.2 (3.1)	2–12	0.25
Boston Naming Test (15)	8.8 (2.6)	4–14	8.8 (2.4)	5–14	0.99
Constructional praxis (11)	5.7 (2.5)	1–11	6.9 (1.4)	5–10	0.09
Immediate total recall (30)	9.0 (3.8)	3–17	8.4 (3.2)	4–14	0.61
Delayed total recall (10)	0.5 (0.9)	0–3	0.5 (0.9)	0–2	0.96

[a]SD, standard deviation; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

Table 2

Coefficients (standard errors) of multiple regression analyses examining the relationship between the presence of ApoE ε4 and cognitive performance[a]

	Presence of ε4 (0 = no, 1 = yes)	Age (yr)	Education (yr)	Vascular comorbidity (0= no, 1 = yes)
Mattis Dementia Rating Scale				
Total score	−0.94 (5.02)	−0.06 (0.35)	1.31 (0.57)	−5.94 (5.61)
Attention	−0.22 (1.15)	0.08 (0.08)	0.24 (0.13)	−1.05 (1.30)
Initiation/perseveration	1.73 (2.18)	0.02 (0.15)	0.11 (0.26)	−2.28 (2.50)
Construction	−0.63 (0.46)	0.00 (0.03)	0.12 (0.05)	−0.51 (0.52)
Memory	0.06 (0.94)	0.05 (0.07)	0.28 (0.11)	0.93 (1.08)
Conceptualization[b]	−0.69 (1.83)	−0.20 (0.13)	0.56 (0.21)[b]	−3.04 (2.10)
CERAD				
Animal fluency	0.88 (0.96)	−0.04 (0.07)	0.16 (0.11)	0.66 (1.08)
Boston Naming[c]	−0.15 (0.76)	−0.10 (0.05)	0.15 (0.09)	1.66 (0.83)[c]
Constructional praxis[b]	−1.57 (0.62)[b]	0.02 (0.04)	0.32 (0.07)[b]	−0.24 (0.69)
Word list: immediate total recall[b]	0.14 (1.05)	−0.06 (0.08)	0.42 (0.12)[b]	1.28 (1.18)
Word list: delayed recall	0.05 (0.29)	−0.01 (0.02)	0.02 (0.03)	0.51 (0.32)

[a] Coefficients interpreted if the overall model was significant; CERAD; Consortium to Establish a Registry for Alzheimer's Disease.

[b] $P \leq 0.01$.

[c] $P \leq 0.05$.