No Association Between Apoε4 , HIV Infection, Age, Cognitive Outcome or Death

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Abstract

Background: The ε4 allele of the ApoE gene may have important interactions with physical health and cognitive function among individuals with HIV disease. The purpose of this study is to examine the relationships between ε4, HIV disease, age, incident neuropsychological impairment and death in a large, well characterized study sample.

Methods: Among the men participating in the Multicenter AIDS Cohort Study (MACS) 2,846 had ApoE genotyping and neuropsychological test data available for analysis. Classifications of cognitive impairment were operationalized using the criteria outlined by Woods et al. (2004) and Antinori et al. (2007). We examined the unadjusted associations between ApoE and other variables using t-tests and contingency tables. Time to death or incident cognitive impairment was tested using Cox proportional hazard models.

Results: There was a significant association between race and ApoE genotype; 23.2% of the men who identified themselves as White had at least one copy of the ε4 allele, whereas 31.2% of the men in other races (primarily African-American) had at least one ε4 allele. We found a significant association between time to death and HIV infection status, as well as older age, race, and education; ApoE status was not significantly associated with time to death. We found a significant association between HIV infection and time to incident cognitive impairment, as well as age, and education; Apoε4 status was not related to incident cognitive impairment. There were no significant two-way interactions between ApoE, HIV, and age on cognitive impairment.

Conclusions: Our analysis found no association between ApoE genotype and the development of cognitive dysfunction or time to death. This does not preclude the possibility that ApoE may have an impact on specific cognitive functions or cognitive domains; however, our findings indicate that the transition from normal to impaired cognition is unaffected by ApoE ε4. These data replicate and strengthen prior findings of the lack of association between ApoE genotype and cognitive outcomes in HIV disease. We conclude that within the specific constraints of an exclusively male sample in which the majority of participants were younger than 65 years of age, the ApoE ε4 allele does not interact with HIV serostatus.

Methods

Study Participants

The MACS is an ongoing, prospective cohort study of the natural and treated history of HIV infection among men who have sex with men in the United States. We refer to the men who enrolled in 1984-1985 or 1987-1991 as Cohort 1 (C1), and those who enrolled between 2001-2003 as Cohort 2 (C2).

4275 of these men had ApoE genotyping available for this analysis, and 2846 of them also had neuropsychological test data. The individuals who contributed data to these analyses were more likely to represent racial minorities, less likely to be HIV-infected, and more likely to be alive and active in the study as of December 31, 2012, relative to those who did not contribute data.

Methods (Con't)

Genomic DNA extraction

Genomic DNA was isolated from lysates of either buffy-coat or B-cell immortalized cell lines from individuals within the MACS. Genomic DNA concentration and quality was assessed using UV Spectrophotometry and/or by fluorometric quantitation.

Genotyping

End-point genotyping of ApoE variants rs429358 [C/T] and rs7412 [C/T] was performed using TaqMan and OpenArray technologies. Genomic DNA was introduced to nanoliter reaction wells on a high-density microplate containing validated TaqMan primers and probes. PCR amplification was completed as recommended by the manufacturer. Water non-template and known positive controls were plated on each array for internal quality assurance and quality checks. Arrays were imaged after amplification on one of two OpenArray NT imagers. Genotypes were ascribed after clustering VIC and FAM signals.

Neuropsychological Evaluation

The NP evaluation includes measures from multiple cognitive domains related to the classification of HIV-Associated Neurocognitive Disorder (HAND). In order to be classified, an individual needed to have completed at least one test in least four of the six domains. In accordance with the guidelines set forth in the Antinori criteria, we classified individuals as mildly impaired if they had two or more domains with T-scores less than 40. They were classified as severely impaired if they had two or more domains with T-scores less than 30 or one domain score less than 25, and another domain score less than 40. Because we did not assess activities of daily living at the earlier study visits, we were unable to assign HAND classifications, but were nevertheless able to provide evidence of any cognitive deficits.

Statistical Analysis

We examined the unadjusted associations between ApoE genotype and other variables using t-tests and contingency tables as appropriate. Time to event (i.e., death or cognitive impairment) were tested using Cox proportional hazard models. We attempted to identify and account for any differences in association as a function of time of entry into the study (i.e., cohort effects)

Results

There were differences among the men in terms of ApoE ε4 status as a function of race and cohort. The allele frequencies for ApoE among the white participants were: ε2 0.75, ε3 0.80, and ε4 0.13. Among the minority participants, the allele frequencies were: ε2 0.11, ε3 0.72, and ε4 0.18. These rates are comparable with population estimates of the allele distributions: ε2 .085, ε3 .768, and ε4 .147.

In a Cox regression model of time to death, we found a significant effect of HIV Disease (See Figure 1), age, race and cohort – but no effect of ApoE (Table 2).

In a Cox regression model of time to incident cognitive impairment among the men with normal Cognition at study entry, we found effects of age and premorbid IQ, but no effect of HIV disease or ApoE (Table 3). Although the men with HIV Disease did appear to decline faster (Figure 2), the effect was not statistically significant.

Table 1: Descriptive Statistics by Cohort, Race, and ε4 Status

Cohort	1				2			
Race	Minority		White		Minority		White	
ε4 Status	No	Yes	No	Yes	No	Yes	No	Yes
N (%)	231 (70.2)	98 (29.8)	2377 (77.1)	705 (22.9)	342 (65.4)	181(34.6)	262 (76.8)	79 (23.2)
Age	32.09 (7.1)	32.14 (7.1)	33.79 (7.5)	33.55 (7.6)	38.29 (8.6)	39.02 (8.6)	36.78 (10)	38.47 (9.8)
Study Status[1]	31.60/35.93/32.47 (73/83/75)	26.53/36.73/36.73 (26/36/36)	33.40/32.56/33.95 (796/774/807)	34.04/30.50/35.46 (240/215/250)	77.19/14.91/7.89 (264/51/27)	74.03/20.99/4.97 (134/38/9)	82.82/14.50/2.67 (217/38/7)	82.82/17.72/0.00 (65/14/0)
HIV Infected[2]	51.08 (118)	50.00 (49)	34.29 (815)	34.33 (242)	57.60 (197)	58.01 (105)	46.95 (123)	50.63 (40)
AIDS[2]	23.38 (54)	22.45 (22)	28.19 (670)	31.21 (220)	6.43 (22)	7.18 (13)	3.44 (9)	2.53 (2)
AIDS Deaths[2]	81.33 (61)	80.56 (29)	80.42 (649)	84.40 (211)	29.63 (8)	55.56 (5)	28.57 (2)	0.00 (0)
cART [2](% of HIV+)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	65.48 (129)	70.48 (74)	65.85 (81)	80.00 (32)
Education (Years)	15.54 (2.4)	15.15 (2.5)	15.96 (2.3)	15.93 (2.4)	13.06 (2.3)	12.96 (2.2)	15.53 (2.9)	15.12 (2.7)
CESD	10.93 (9.5)	9.96 (6.8)	9.57 (8.6)	9.49 (8.4)	14.83 (12)	15.42 (12)	12.78 (11)	11.81 (12)
Neuro Outcome Ever[2]	30.83 (37)	38.78 (19)	46.71 (674)	48.83 (209)	59.18 (187)	67.65 (115)	43.44 (106)	43.42 (33)

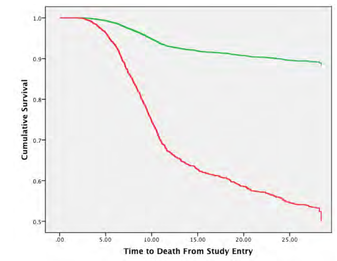


Table 2: Cox Regression Models of Time to Death Hazard Ratios and 95% Confidence Interval

	Model 1	Model 2	Model 3
Age at Entry	1.02 (1.01-1.03) *	1.02 (1.01-1.03) *	1.03 (1.02-1.05) *
Race (Caucasian)	2.50 (1.9-3.2) *	2.50 (1.9-3.2) *	1.71(1.3-2.2) *
HIV Infected	4.96 (4.2-5.9) *	4.96 (4.2-5.9) *	5.50 (4.6-6.6) *
ApoE ε4 (present)		.99 (.82-1.2)	1.01(.84-1.2)
Cohort (C2)			.24 (.16-.32) *

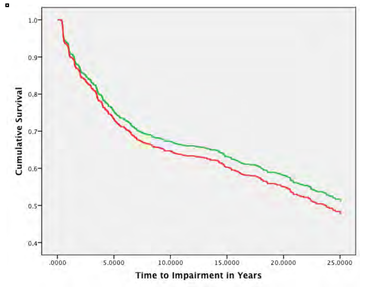


Table 3: Cox Regression Models of Incident Cognitive Impairment Hazard Ratios and 95% Confidence Interval

	Model 1	Model 2	Model 3
Age	1.03 (1.02-1.04) *	1.03 (1.02-1.04) *	1.03 (1.02-1.04) *
Education (Years)	1.02 (.98-1.05)	1.02 (.98-1.05)	1.02 (.98-1.05)
Shipley IQ	.97 (.96-.98) *	.97 (.96-.98) *	.97 (.96-.98) *
Race (Caucasian)	1.15 (.93-1.4)	1.15 (.93-1.4)	1.14 (.91-1.4)
HIV Infected	1.10 (.93-1.3)	1.10 (.93-1.3)	1.10 (.94-1.3)
ApoE ε4 (Present)		1.08 (.90-1.3)	1.07 (.90-1.3)
Cohort (C2)			.95 (.76-1.2)

Discussion

Although we found a significant increase in the rate of ε4 among non-white participants (primarily African-American), once we controlled for race, we found no significant associations between ApoE genotype and either HIV infection, age, death, or neuropsychological dysfunction. In particular, our analysis of incident neuropsychological impairment among those men who were classified as cognitively normal at their first NP study visit found no association between ApoE genotype and the development of cognitive impairment.

Our failure to find an association between ApoE genotype, age, and cognitive impairment is at odds with some reports. However, the discrepancy may be, in part, due to the fact that these other reports have detailed cross-sectional analyses which may be affected by selective survival (i.e., the older infected men may be more likely to have had a longer history of uncontrolled HIV replication and thus entered any study with greater degree of CNS involvement). Our longitudinal analysis of time to develop impairment from the state of normal cognition thus strengthens the conclusions by others that at least within the age band tested (i.e., primarily younger than 65 years) Apoε4 genotypes not differentially affecting HIV-infected individuals.