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Association of Apolipoprotein E-e4 and Dementia Declines with Age

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Abstract

Objective—To study the association of dementia with APOE-e4 and its interaction with age in a nonagenarian Costa Ricans (N-sample) and a general elderly contrast group (GE-sample).

Methods—In both case-control studies, participants were cognitively intact or demented. The N-sample (N=112) was at least age 90; the GE-sample (N=98) was at least age 65.

Results—Dementia and APOE-e4 were not significantly associated in the N-sample, but were in the GE-sample. There was a significant interaction of age with APOE-e4 in the N-sample, but not in the GE-sample. Descriptively dividing the N-sample at the median (age 93) showed a group

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interaction: APOE-e4 was more associated with dementia in the younger N-sample than in the older N-sample, where six of seven APOE-e4 carriers were cognitively intact.

Conclusions—The results support the reduction in association of APOE-e4 with dementia in extreme old age, consistent with a survivor effect model for successful cognitive aging.

Keywords

Successful cognitive aging; oldest-old; dementia risk factors

OBJECTIVE

Disease is usually investigated as an exception from non-diseased normality, but a third status is resistance to disease. Studies of disease resistance may be less common because distinguishing resistant individuals is more difficult than identifying disease. However, resistance is especially plausible if there is a low rate of the disease despite high risk.

The apolipoprotein E-e4 allele (APOE-e4) is a risk factor for dementia and cardiovascular disease (6). Many cardiovascular risk factors have been associated with risk for dementia in studies on samples averaging below age 75 (7). In older samples, some of these cardiovascular risk factors – including APOE-e4 – have less risk for dementia. A study pooling 40 samples from around the world found a reduced risk of APOE-4 with increasing age (2), and a study of Cache County, Utah residents found a significant age by APOE-e4 interaction for e4 homozygotes (4).

The present study examined the effect of APOE-e4 in a case-control sample of nonagenarians (N-sample) from the Central Valley of Costa Rica (CVCR), which is relatively culturally and environmentally homogeneous. As a contrast, we also included an independent general elderly CVCR sample (GE-sample, above age 65). The CVRC includes 70% of the Costa Rica's population, which possesses among the highest life expectancies in the world (8). In addition, the elderly in the CVCR have reduced genetic heterogeneity (9), making it attractive for genetic studies.

METHODS

Selection of Both Samples

The two samples used here were collected independently and had different lower age requirements: the N-sample included those at least age 90; the GE-sample included participants at least age 65. Both sets of participants were assessed by the same geriatrician (DV), using the same criteria to classify dementia and no cognitive impairment, and all were native to the CVRC. Eligibility for both samples included CVCR birth, Alzheimer's type dementia following DSM-IV criteria or intact cognition excluding any evidence cognitive change. Both samples excluded participants with cognitive impairment without dementia, a history of stroke, or the presence of a potentially dementing disease other than Alzheimer's disease (AD). IRB approvals were obtained, with informed consent signed by all participants (or proxies, if demented without capacity). All participants were directly

examined, with a close relative or caregiver informant providing additional clinical information.

N-sample

Costa Rican Association of Geriatricians physicians referred potential participants at least 90 years old to DV for clinical dementia evaluation including direct and informant assessment on Clinical Dementia Rating (CDR). Four fifths of these participants were patients at Blanco Cervantes National Hospital for Geriatrics and Gerontology, which serves over 80% of Costa Ricans above age 60. In this study of successful cognitive aging, subject selection aimed for a two-thirds cognitively intact sample (3).

GE-sample

All participants were ascertained at Blanco Cervantes hospital, with no overlap with the N-sample. Direct clinical evaluation and informant assessment were conducted by DV on approximately equal subsamples of cognitively intact and demented at least age 60. In the present study, the lower age limit was restricted to age 65, a more conventional age threshold for at-risk individuals, yielding 53 eligible demented cases and 45 cognitively intact controls.

APOE Genotyping

APOE genotype was determined from blood sample DNA. Participants with at least one APOE-e4 allele were called APOE-e4 carriers.

Stepwise Logistic Regression Analyses

In each sample, step-wise logistic regression was used to assess the association of dementia with APOE-e4 and the interaction of APOE-e4 with age. Step one included age, sex and years of education. Step two included APOE-e4. Step three included the APOE-e4 by age interaction.

The two samples were also compared on the association of APOE-e4 with dementia, and then too by their respective interactions with age. Step one included covariates: sex and years of education, and the variables to be included in the interaction in the subsequent step: APOE-e4 and the sample. Age was not included as an initial covariate, since the two samples differed greatly. Step two included the interaction of APOE-e4 and the sample. Step three included the variable and interactions necessary to perform the subsequent step: age and its interactions with sample and with APOE-e4. Step 4 included the interaction of the sample, APOE-e4 and age. This last step tested whether the age by APOE-e4 interaction differed in the two samples.

RESULTS

The Table compares demographic and APOE characteristics of demented and cognitively intact participants in the N-sample (N=112) and the GE-sample (N=98). In the N-sample, dementia was associated with being female. In the GE-sample, dementia was associated

with carrying an APOE-e4 allele. Age was not significantly associated with dementia in either sample.

Logistic regression for each sample evaluated the association of dementia with APOE-e4, and its interaction with age. In the N-sample, dementia was not significantly associated with APOE-e4 (X^2=2.47, df=1, p=0.12; OR=2.43, 95% CI=0.81, 7.32), but in the GE-sample, dementia was significantly associated with APOE-e4 (X^2=12.35, df=1, p<0.001; OR=7.03, CI=2.07, 23.82). In contrast, in the N-sample there was a significant interaction of age and APOE-e4 (X^2=4.47, df=1, p=0.03), but the interaction of age and APOE-e4 was not significant in the GE sample (X^2=1.43, df=1, p=0.23).

In logistic regression comparing the two samples, the associations of dementia with APOE-e4 in each sample did not differ significantly (X^2=1.40, df=1, p=0.24), nor did the difference in the interactions of age with APOE-e4 (X^2=1.63, df=1, p=0.20).

The significant interaction between age and APOE-e4 within the N-sample makes the interpretation of the nonsignificant main effect of APOE-e4 problematical. We described the impact of age within the N-sample by dichotomizing it at the median, age 93. There were 54 participants with age<93: 17 cases (10 without APOE-4, 7 with APOE-e4), and 44 cognitively intact participants (34 without APOE-e4, 10 with APOE-e4). There were 58 participants with age ≥93: 20 cases (19 without APOE-e4, 1 with APOE-e4), and 38 cognitively intact participants (32 without APOE-e4, 6 with APOE-e4). In logistic regression controlling for age, sex, and years of education, the association between APOE-e4 and increased risk of dementia was significant in the younger N-sample (X^2=8.46, df=1, p=0.004; OR=9.2, 95% CI=1.8, 46.2). In contrast, APOE-e4 was associated with reduced risk of dementia in the older N-sample, but this was not significant (X^2=1.15, df=1, p=0.28; OR=0.33, 95% CI=0.03, 3.08). The difference between the two subgroups in the effect of APOE-e4 on dementia was significant (X^2=7.40, df=1, p=0.007).

DISCUSSION

Many studies of the elderly have demonstrated an association of APOE-e4 with risk of dementia, as was found in the GE-sample. This association, however, gradually diminishes with age (2). In the N-sample, there was a significant interaction of APOE-e4 and age with risk of dementia. Even in the younger N-sample, risk for dementia was significantly associated with APOE-e4. In contrast, in the older N-sample, there is a nonsignificant association of reduced risk for dementia with APOE-e4; six out of the seven APOE-e4 carriers were cognitively intact.

This study was limited by the recruitment strategies of the two CVCR samples, not only restricted to either cognitively intact or demented participants, with cognitively impaired but not demented participants excluded, but also by the imposition of different proportions of demented participants in these modest samples. These samples, especially the N-sample, are survivors, who may differ from those with early mortality. The APOE-e4 allele is also a risk factor for cardiovascular disease and mortality (6), so its frequency tends to diminish with increasing age. The lower rate of APOE-e4 carriers in the N-sample (15%), compared with

the GE-sample (27%) reflects this. A strength of this study is the relatively genetically and culturally homogeneous population from which the samples were drawn.

For a few cardiovascular risk factors, the diminishing risk of dementia with increasing age progresses to reversal for sufficiently elderly participants (5). Consistent with this, in a study of cognitively intact Puerto Rican nonagenarians, neuropsychological performance was better in APOE-e4 carriers (1).

To explain such a reversal, in a survivor effect model for successful cognitive aging, there is a risk factor for both mortality and dementia, but a relatively small group has protection against it (10). At increasing ages, the proportion of protected survivors among those remaining free of dementia increases. For such a risk factor, the overall association with risk of dementia is an average of the strong association among unprotected survivors and the weak association among protected survivors. Thus, at increasing ages, this association decreases due to the increasing proportion of protected survivors. The reduced association of dementia with APOE-e4 with increasing age within the N-sample is consistent with this survivor effect model. Studies specifically focused on the identification of factors that promote successful cognitive aging should be aimed at individuals carrying a well-established risk factor for dementia and yet have reached extreme old while remaining cognitively intact.

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Table

Demographic and APOE genotype characteristics of demented and cognitively intact subjects in the nonagenarian (N-) and the general elderly (GE-) samples.

Variable	Participants with Dementia	Cognitively Intact Participants	Statistic (df)	p-value
N-Sample	N = 37	N = 75		
Age, mean (SD)	93.4 (3.5)	93.4 (3.3)	t = 0.01 (110)	0.99
Female, N (%)	32 (86)	51 (68)	X^2 = 4.41 (1)	0.04
Years of education, mean (SD)	3.5 (2.3)	3.4 (3.0)	t = 0.51 (110)	0.61
APOE genotype, N (%)				
e2/e2	0 (0)	0 (0)		
e2/e3	0 (0)	4 (5)		
e2/e4	0 (0)	1 (1)		
e3/e3	29 (78)	62 (83)		
e3/e4	7 (19)	8 (11)		
e4/e4	1 (3)	0 (0)		
Presence of APOE-e4 allele, N (%)			X^2 = 1.78 (1)	0.18
e4	8 (22)	9 (12)		
no e4	29 (78)	66 (88)		
GE-sample	N=53	N=45		
Age, mean (SD)	80.9 (6.5)	78.6 (6.9)	t = 1.65 (96)	0.102
Female, N (%)	40 (76)	32 (71)	X2 = 0.24 (1)	0.63
Years of education, mean (SD)	5.2 (4.1)	3.9 (2.3)	t = 1.92 (96)	0.06
APOE genotype, N (%)				
e2/e2	1 (2)	3 (7)		
e2/e3	1 (2)	0 (0)		
e2/e4	0 (0)	0 (0)		
e3/e3	31 (59)	38 (84)		
e3/e4	20 (38)	4 (9)		
e4/e4	0 (0)	0 (0)		
Presence of APOE-e4 allele, N (%)			X2 = 10.95 (1)	0.001
e4	20 (38)	4 (9)		
no e4	33 (62)	41 (91)		