Apolipoprotein E ϵ4 and the Risk of Dementia With Stroke

A Population-Based Investigation

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Objective.—To investigate the association between the apolipoprotein E (*APOE*) genotypes and dementia in patients with stroke, defined as either vascular dementia (VaD) or Alzheimer disease with cerebrovascular disease (AD with CVD).

Design and Setting.—Population-based, case-control study from Rotterdam, the Netherlands, and New York City.

Participants.—A total of 187 patients with dementia and stroke were compared with 507 controls similar in age and ethnic group.

Main Outcome Measures.—The *APOE* allele frequencies in patients and controls; the odds ratio of dementia with stroke, VaD, and AD with CVD, adjusted for age, sex, residency, and education; and the percent attributable risk related to the *APOE* ϵ4 allele.

Results.—Overall, patients with dementia and stroke had a higher *APOE* ϵ4 allele frequency than controls. Compared with *APOE* ϵ3 homozygote individuals, *APOE* ϵ4 homozygotes had a 7-fold increased risk of dementia with stroke (OR=6.9; 95% CI, 1.6-29.4), while *APOE* ϵ4 heterozygotes had nearly a 2-fold increase in risk (OR=1.8; 95% CI, 1.2-2.7). Risks associated with *APOE* ϵ4 were elevated regardless of the subtype of dementia with stroke or age or sex. The percent attributable risk related to the *APOE* ϵ4 allele among demented patients with stroke was 41% overall, 33% among those with VaD, and 44% among those with AD with CVD.

Conclusion.—The *APOE* ϵ4 allele is a genetic risk factor for dementia with stroke, including VaD and AD with CVD. This may imply shared genetic susceptibility to dementia associated with stroke and AD. Alternatively, the category of patients with dementia and stroke, including VaD as currently defined, may include patients with AD.

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THE ELEVATED risk of Alzheimer disease (AD) among individuals with the ϵ4 allele of the apolipoprotein E gene (*APOE* indicates the gene, APOE indicates the protein) has been confirmed in many populations.[1-5] Among patients with dementia and stroke, the role of *APOE* remains uncertain.[6-12] Many studies have been limited by small numbers of patients and other methodological issues. The aim of this population-based, case-control study was to examine the relationship between the *APOE* genotypes and dementia with stroke or its subtypes, vascular dementia (VaD) and AD with cerebrovascular disease (AD with CVD), in Rotterdam, the Netherlands, and New York City, while considering the effects of age, sex, and ethnic origin.

METHODS

Data were pooled from individuals participating in 2 population-based studies: Rotterdam and New York City (the Washington Heights neighborhood). Informed consent was obtained from all participants, and the study was approved by the local medical ethics committees and the institutional review board.

The Rotterdam study was a population-based cohort study of the total population in a suburb, aged 55 years and older, including institutionalized persons. The objective was to investigate determinants of chronic disabling diseases of the cardiovascular and nervous system.[13] The cohort included 7983 subjects (response rate, 78%) who were examined from 1990 to 1993. In 1993 and 1994, 88% of the participants who were alive (n=6315) were reexamined. Cognitive performance was assessed by the Mini-Mental State Examination and by the Geriatric Mental State schedule. Dementia was diagnosed using a 3-phase design, as described elsewhere.[14] Diagnosis included an interview with a relative, neuropsychological testing, an examination by a behavioral neurologist, and a magnetic resonance imaging scan.

The Washington Heights study consisted of a random sample of Medicare recipients in northern New York City provided by the Health Care Financing Administration. The objective of this investigation was to estimate the frequency of various age-related diseases

of the nervous system and identify determinants of disease. The response rate was 72% and did not differ from nonresponders by ethnic origin. The 2250 participants underwent an annual assessment. A physician elicited the medical history and conducted a standardized neurological examination. A standardized neuropsychological battery[15,16] and assessment of activities of daily living were used to ascertain cognitive and functional criteria for dementia.

Diagnosis

All information was reviewed at consensus conferences in either Rotterdam or New York. A panel of clinicians arrived at consensus for diagnosis of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders* definition.[17] The diagnosis of stroke was implemented similarly in Rotterdam and New York using the World Health Organization criteria.[18] At both sites, direct questioning of the next of kin or caregiver established the diagnosis of stroke, supplemented by neurological examination and brain imaging. The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke–the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[19] A diagnosis of dementia with stroke was considered for all patients with dementia with a history or clinical evidence of stroke, and further subdivided into the following groups: VaD, AD with CVD, or dementia with stroke-unclassified. Vascular dementia was based on the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) and was distinguished from AD when the onset of dementia occurred within 3 months after the stroke or when there was an abrupt change or a stepwise decline in cognitive function.[20] A diagnosis of AD with CVD was based on a history or clinical evidence of stroke (including brain imaging), judged not to be the cause of dementia, in patients who would have otherwise met criteria for AD. A diagnosis of dementia with stroke-unclassified was made when limited information was available, such as the absence of brain imaging (n=3), or in the absence of a temporal relationship between dementia and stroke (n=24). All diagnoses were made without knowledge of the *APOE* genotype.

Study Population

Included were patients with dementia and stroke. The participants from the Washington Heights study also included 2 patients with VaD confirmed by autopsy. Excluded were patients with AD alone or dementia due to other causes. The comparison group consisted of a random sample of individuals without dementia in the Rotterdam and Washington Heights studies for whom DNA samples were available. For every case, approximately 3 controls were matched on both age (10-year interval) and ethnic group. Among Hispanics, there were too few controls older than 85 years; thus, all available controls were included with adjustments made in the analysis. This resulted in a study population of 187 patients with dementia and stroke and 507 controls.

There were no African Americans or Hispanics in the Rotterdam study. In Washington Heights, individuals were classified as African American, white (both non-Hispanic), or Hispanic groups by standardized, direct interview[21] with the individual or a family member.

Table 1.—Description of Study Population*

Variables	Dementia With Stroke (n=187)†	Vascular Dementia (n=90)	AD With CVD (n=70)	Controls (n=507)
Age, mean (SD), y	80.1 (7.6)	79.1 (8.1)	80.2 (7.1)	76.8 (7.1)‡
Sex, No. (%)				
Men	51 (27)	29 (32)	16 (23)§	202 (39.8)
Women	136 (73)	61 (68)	54 (77)§	305 (60.2)
Residency, No. (%)				
New York	96 (51)	44 (49)	40 (57)	301 (59)
Rotterdam	91 (49)	46 (51)	30 (43)	206 (41)
Ethnicity, No. (%)				
White	97 (51.5)	48 (53)	34 (48.6)	292 (57.6)
African American	35 (19)	15 (17)	19 (27)	77 (15.2)
Hispanic	54 (29)	27 (30)	16 (23)	138 (27.2)
Asian	1 (0.5)	0 (0)	1 (1.4)	0 (0)
Education, mean (SD), y	7.2 (3.6)	7.0 (4.0)	7.8 (3.4)	9.2 (3.9)‡

*AD with CVD indicates possible Alzheimer disease with cerebrovascular disease.
†Includes 26 patients with "unclassified" dementia with stroke.
‡The controls were younger and better educated than the cases, $P<.001$.
§The proportion of men and women were slightly different in the AD with CVD group compared with the others, $P<.05$.

Laboratory Analysis

Genotypes were performed using a polymerase chain reaction, using methods as previously described.[4,5,22,23]

Statistical Analysis

APOE allele frequencies were determined by counting alleles and calculating sample proportions. Normally distributed, continuous data were studied using an analysis of variance (ANOVA) model, and the χ^2 test was used for categorical data. The relative risk (RR) of dementia with stroke, VaD, or AD with CVD was estimated as an odds ratio (OR) in a multiple logistic regression analysis, and presented with a 95% confidence interval (CI) using *APOE* ϵ3/ϵ3 as the reference. To adjust for confounding, we added age and residency (Rotterdam or New York City), sex, and education to the model. Logistic regression analyses were also performed stratified by age, sex, ethnic group, and residency. Logistic regression models were evaluated by goodness-of-fit tests. We estimated the proportion of dementia with stroke among individuals with an *APOE* ϵ4 allele: the percent attributable risk.

RESULTS

Characteristics of the patients and controls are outlined in Table 1 (Rotterdam, N=297; New York, N=397). The distribution of the *APOE* alleles in the controls from Rotterdam did not differ from those in New York (Rotterdam: *APOE* ϵ2, 0.092; *APOE* ϵ3, 0.769; and *APOE* ϵ4, 0.138 vs New York: *APOE* ϵ2 0.081; *APOE* ϵ3, 0.784, and *APOE* ϵ4, 0.135; $\chi^2=0.43$, $df=2$, $P=.81$), nor did the distribution of the *APOE* alleles differ among patients with dementia and stroke (Rotterdam: *APOE* ϵ2, 0.071; *APOE* ϵ3, 0.709; and *APOE* ϵ4, 0.220 vs New York: *APOE* ϵ2, 0.078; *APOE* ϵ3, 0.729, and *APOE* ϵ4, 0.193; $\chi^2=0.4$, $df=2$, $P=.83$). The distribution of patients with dementia and stroke, as well as the subtypes, did not differ significantly by location (Rotterdam: AD with CVD, 33%; VaD, 51%; unclassified, 16% vs New York: AD with CVD, 41%; VaD, 46%; unclassified, 13%; $\chi^2=1.7$, $df=2$, $P=.45$) or by ethnic group (white: AD with CVD, 35%; VaD, 50%; unclassified, 15%; African American: AD with CVD, 54%; VaD, 43%; unclassified, 3%; Hispanic: AD with CVD, 30%; VaD, 50%; unclassified, 20%; $\chi^2=10.3$, $df=6$, $P=.28$). Moreover, the *APOE* allele frequencies did not differ by subtype of dementia (AD-with CVD: *APOE* ϵ2, 0.071; *APOE* ϵ3, 0.729; and *APOE* ϵ4, 0.2 vs VaD: *APOE* ϵ2, 0.072; *APOE* ϵ3, 0.722; and *APOE* ϵ4, 0.206; $\chi^2=0.5$, $df=4$, $P=.93$). Since allele frequencies did not differ by site and diagnosis did not differ by race (which was unevenly distributed be-

Table 2.—Odds Ratio for Dementia With Stroke Associated With *APOE* Genotype*

APOE Genotype	Total No. With Dementia With Stroke (OR [95% CI])	No. With Vascular Dementia (OR [95% CI])	No. With AD and CVD (OR [95% CI])	No. of Controls
ϵ3/ϵ3	92 (1 [reference])	48 (1 [reference])	33 (1 [reference])	302
ϵ2/ϵ2	0 . . .	0 . . .	0 . . .	2
ϵ2/ϵ3	24 (1.1 [0.7-1.9])	10 (0.9 [0.4-1.9])	10 (1.3 [0.6-3.3])	68
ϵ2/ϵ4	4 (0.9 [0.3-2.9])	3 (1.2 [0.3-4.5])	0 . . .	15
ϵ3/ϵ4	61 (1.8 [1.2-2.7])†	24 (1.3 [0.8-2.2])	26 (2.2 [1.2-3.8])	117
ϵ4/ϵ4	6 (6.9 [1.6-29.4])‡	5 (10.5 [2.4-46.6])‡	1 (3.3 [0.4-34.3])	3

*OR indicates odds ratio; CI, confidence interval; and AD, Alzheimer disease. Relative risk estimated as OR with adjustment for age, sex, residency, and education. The total for the dementia with stroke group includes 27 patients who could not be classified as having either vascular dementia or possible AD with cerebrovascular disease (CVD) as well as patients with vascular dementia and possible AD with CVD.

† $P<.05$.

‡ $P<.005$.

tween sites), we pooled the data from the 2 sites.

The distribution of *APOE* genotypes was similar in patients with prevalent and incident disease. Distribution of prevalent (n=126) and incident (n=61) *APOE* alleles were as follows: ϵ4/ϵ4: 3.9% and 3.3%; ϵ3/ϵ4: 32.5% and 29.5%; ϵ3/ϵ3: 46.1% and 49.2%; ϵ2/ϵ4: 2.4% and 3.3%; ϵ2/ϵ3: 15.1% and 14.7%; and ϵ2/ϵ2: 0% and 0%, respectively ($\chi^2=2.1$, $df=4$, $P=.72$). Since these groups were significantly distributed, these groups were also combined. This resulted in a study population of 187 patients with dementia and stroke, subclassified as follows: 2 patients (1%) with definite VaD, 18 (10%) with probable VaD, 72 (39%) with possible VaD, 70 (37%) with AD with CVD, and 27 (13%) who could not be classified as either VaD or AD with CVD. The control group consisted of 507 nondemented individuals frequency matched by 10-year age interval and ethnic group (Table 1). However, patients with dementia were still older and less well educated than controls. There were also more women among the patients than controls. The distribution of the *APOE* genotypes in patients and controls were in Hardy-Weinberg equilibrium suggesting no selective inbreeding or survival.

The frequency of the *APOE* ϵ4 allele was significantly higher in patients with dementia with stroke compared with the controls (controls: *APOE* ϵ2, 0.086, ϵ3, 0.778, ϵ4, 0.136 vs dementia with stroke: *APOE* ϵ2, 0.075, ϵ3, 0.719, ϵ4, 0.206; $\chi^2=10.2$, $df=2$, $P=.006$). Compared with *APOE* ϵ3/ϵ3, the OR for dementia with stroke, including VaD and AD with CVD, associated with *APOE* ϵ4 homozygosity was increased nearly 7-fold (OR=6.9; 95% CI, 1.6-29.4, $P<.008$ [Table 2]), while the OR associated with *APOE* ϵ4 heterozygosity was increased nearly 2-fold (OR=1.8; 95% CI, 1.2-2.7; $P<.004$ [Table 2]). Adjustment for age, ethnic group, or study site did not change the ORs.

Overall, the percent attributable risk or proportion of dementia with stroke among individuals with an *APOE* ϵ4 allele was 41% (95% CI, 37%-44%); in VaD the percent attributable risk was 33% (95% CI, 29%-38%); and in AD with CVD the percent attributable risk was 44% (95% CI, 39%-48%).

APOE ϵ4 allele frequency and RR associated with at least 1 *APOE* ϵ4 allele did not change with increasing age. The *APOE* ϵ4 frequency among demented patients with stroke was similar in women (0.210) and men (0.196). No effects of the *APOE* ϵ2/ϵ3 genotype were observed.

The relationship between the *APOE* ϵ4 allele and dementia in patients with stroke did not vary by study site or subtype of dementia (VaD or AD with CVD [Table 2]). However, among African Americans and Hispanics, the OR for dementia with stroke associated with *APOE* ϵ4 homozygosity was high (OR=10.7; 95% CI, 1.1-80.4; $P<.002$), while the OR associated with *APOE* ϵ4 heterozygosity was only slightly increased (OR=1.3; 95% CI, 0.7-2.4). Among whites, the OR for dementia with stroke associated with *APOE* ϵ4 homozygosity and heterozygosity were both increased (OR=3.9 and 2.2, respectively), but only *APOE* ϵ4 heterozygosity was statistically significant (OR=2.2; 95% CI, 1.8-3.9; $P<.007$) due to the small number of white homozygotes (OR=3.9; 95% CI, 0.6-28.7).

COMMENT

An increased risk of dementia with stroke, which included patients with either VaD or AD with CVD, was found to be associated with the *APOE* ϵ4 allele. The association between the *APOE* ϵ4 allele and dementia with stroke was similar in women and men and did not vary with increasing age. The *APOE* ϵ4 allele was associated with a higher RR of dementia with stroke in both the homozygous and heterozygous configuration, but among African Americans and Hispanics the strongest effect was observed in those individuals homozygous for *APOE* ϵ4. No effects of the *APOE* ϵ2 allele were apparent.

We pooled data from 2 population-based studies because prior studies had included too few patients and controls to investigate the relationship between *APOE* and dementia with stroke. The distribution of the *APOE* alleles and the subtypes of dementia with stroke were similar in 2 cities, lessening the possibility that the results reflect admixture of genetically distinct populations. Nevertheless, all analyses were adjusted for residency and ethnic group. Although autopsy confirmation was limited to 2 patients, the diagnostic workup in both populations was relatively complete. More extensive neuropathological examination will be essential to increase the diagnostic certainty and to further clarify the association between *APOE* ϵ4 and dementia with stroke.

Previous investigators[9-12] used criteria other than the NINDS-AIREN.[20] The inconsistency of the association in earlier studies may also have been related to the use of hospitalized patients and controls that did not reflect the patient population.[9-11] One study[12] was population-based and limited the subject pool to stroke survivors as was done in this study. Alternatively, some of the differences between this study and others might reflect the presence of other genetic or environmental risk factors that modify *APOE* ϵ4. *APOE* ϵ2 frequency was previously associated with VaD,[10] but several studies[7-9,12] have found no effect of this allele.

Studies of stroke and *APOE* have also been inconsistent. Patients with ischemic stroke have been reported to have both a higher *APOE* ϵ2 frequency[24] and *APOE* ϵ4 frequency[25] than controls, but others have found no association between the *APOE* genotype and stroke.[26] Although the occurrence of a stroke seems unrelated to *APOE* genotype, the outcome after intracerebral hemorrhage may be worse for individuals with an *APOE* ϵ4 allele.[27]

Our results imply that individuals who develop dementia with stroke, either as VaD or AD with CVD, and those who develop AD may share genetic susceptibility. The APOE protein may be activated in the response to cerebral ischemia[28] and it may function in compensatory synaptogenesis.[29] Alternatively, the APOE protein may be involved in the pathogenesis of VaD or AD with CVD through its effects on lipids. Compared with APOE3, APOE4 increases total cholesterol and low-density lipoprotein cholesterol levels, which could increase the risk of atherosclerotic vascular disease; APOE2 has the opposite effect.[30]

Cerebrovascular disease and AD are common disorders and it is not surpris-

ing that they may overlap in some individuals.[31] This study is limited in that only 2 individuals were autopsied, although imaging studies were performed on all but 3 patients with dementia. Based on previous studies of autopsies of patients diagnosed with VaD, up to one third may also meet criteria for AD.[32]

The *APOE* ϵ4–related risk of dementia and stroke was slightly different in whites than in other ethnic groups paralleling our work in AD.[5] We previously proposed that in African Americans and Hispanics a modifying gene or environmental factor might alter the effects of 1 *APOE* ϵ4 allele, but fails to protect against the consequences of 2 *APOE* ϵ4 alleles.[5]

We conclude that *APOE* ϵ4 is a genetic risk factor for dementia in patients with stroke, including the subcategories of VaD and AD with CVD. The degree of association may vary by ethnic group. To further elucidate the pathogenesis of these types of dementia, the role of vascular risk factors and disease should be studied in relation to the *APOE* genotype. Furthermore, additional genetic susceptibility or modifier loci as well as environmental factors should be investigated.

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