Apolipoprotein E ε4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging

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Abstract

**Background:** Apolipoprotein E (ApoE) ε4 genotype is a well-established risk factor for Alzheimer’s disease (AD). However, its effect on predicting conversion from normal to “cognitive impairment, no dementia” (CIND) and from CIND to AD is less clear.

**Methods:** We used a nested case–control design from the population-based Canadian Study of Health and Aging (CSHA) to examine the effect of ApoE ε4 genotype on the conversion of subjects from normal to CIND and from CIND to AD. We also contrasted these findings with incident cases of AD and vascular dementia (VaD) in the CSHA cohort.

**Results:** The ApoE ε4 genotype was a significant risk factor for conversion from CIND to AD and from normal to AD and VaD. However, it was not a significant risk factor for conversion from normal to CIND. This effect is robust to adjustment for age, sex and education level. There is significant interaction between the ApoE ε4 genotype and age for AD and for conversion from CIND to AD. No interaction between ApoE ε4 genotype, sex, age, ethnicity and education level was found in other subgroup analyses. The positive predictive value of ApoE ε4 for predicting CIND conversion to AD was 0.48, and the negative predictive value was 0.65.

**Interpretation:** Possession of an ApoE ε4 allele increases the risk of AD developing from CIND. It is also associated with a decrease in the age at onset of AD. Its predictive values do not support its utility as a diagnostic test for predicting progression from CIND to AD, but it may be useful in research studies to enrich study samples that have a higher rate of progression to AD.

Dementia has a profound impact on patients, families, caregivers and society in general. Data from the Canadian Study of Health and Aging (CSHA) show that 252,600 people had dementia in Canada in 1991; probable Alzheimer’s disease (AD) was diagnosed in 64% of those people.1 It was also estimated that the net annual cost to society of care for dementia in Canada in 1991 was over $3.9 billion.1 The prevalence of AD rises exponentially, doubling approximately every 5 years between the ages of 65 and 85.

In recent years, rapid progress in molecular genetics has fostered the discovery of at least 4 genes associated with AD: the amyloid precursor protein (APP), the presenilin-1 gene (PS-1), the presenilin-2 gene (PS-2) and the apolipoprotein E gene (ApoE).2,3 Mutations in APP, PS-1 and PS-2 account for virtually all autosomal dominant inherited early-onset forms of AD. However, this form of AD represents less than 10% of all AD cases. By contrast, ApoE ε4 polymorphism does not cause AD, but it operates as a susceptibility gene or genetic risk factor. The gene exists in 3 different allele polymorphisms — ε2, ε3 and ε4 — in the general population. From previous epidemiological studies, it is estimated that people who carry 1 ε4 allele are 3 times more likely to have AD than those who do not carry any ε4 allele, and those who carry 2 ε4 alleles are 9 times more likely to develop AD than those who do not.4,5 In addition, the ε4 allele appears to exert maximal effect in patients in whom AD is diagnosed between the ages of 55 and 75.6,7 The ApoE ε4 allele also has been implicated as a risk factor for vascular dementia (VaD), but the findings have been inconsistent, with some studies showing positive association4,6 and others not.8–15 Recently, it has been recognized that patients who have “cognitive impairment but no dementia” (CIND) are an important group at risk for dementia. Few studies have examined ApoE ε4 as a predictor for progression from normal to CIND and from CIND to dementia.16–20 To further define the relation between ApoE ε4 polymorphism and the risk of dementia in the Canadian population, we examined ApoE ε4 genotype as a predictor for conversion from normal to CIND and from CIND to AD or VaD using data obtained from the CSHA cohort. We also investigated the role of ApoE ε4 genotype as a risk factor for incident cases of AD and VaD, while controlling for the effects of age, sex and level of education.

**Methods**

The CSHA is a population-based longitudinal cohort (n = 10,263) study of aging and cognition with the primary goal of estimating the prevalence and incidence of dementia in Canada. The initial phase 1 assessment took place in 1991, and the 5-year clinical follow-up assessment for cognitive impairment and dementia was conducted during phase 2 in 1996. Details of the CSHA study methodology have been published previously.1–2 Within the cohort, subjects who came for clinical examinations in either community or institutional settings were asked to donate a DNA sample.
for molecular epidemiological study. There were 1469 subjects who consented for ApoE testing who had no dementia in phase 1 of the study and were clinically examined at the phase 2 assessment. We used a nested case–control design to examine the effect of ApoE ε4 allele polymorphism on predicting progression from normal to CIND and from CIND to AD or VaD. The control subjects consisted of 582 normal subjects who did not show any evidence of cognitive changes over the 2 testing phases. Incident cases of CIND, AD and VaD were identified at the phase 2 follow-up. The diagnostic criteria used for normal, CIND, AD and VaD have been previously published and were adhered to without change in the current study. 27 In brief, subjects were deemed cognitively normal if they did not have any DSM III-R criteria28 after clinical and neuropsychological assessment. Subjects who were identified as having some degree of cognitive impairment on clinical examination and neuropsychological testing but who did not meet the specific DSM III-R criteria for dementia were considered to have CIND. AD was diagnosed by DSM III-R dementia criteria and the NINCDS-ADRDA criteria for possible and probable AD.29 Vascular dementia was diagnosed using ICD-10 criteria30 and clinical criteria.

In addition, 296 subjects in whom CIND was diagnosed at phase 1 were followed to determine the rate of conversion to AD, VaD or other dementia over 5 years, the rate of stable CIND and the rate of reversion to normal. Continuous variables were compared using analysis of variance with post-hoc Tukey analysis, and categorical variables were compared using χ² statistic. The effect of ApoE ε4 on risk of conversion was examined in conjunction with age, sex and years of education, which are known risk factors for AD and may have been potential confounders in the current study. Because certain ApoE genotypes are relatively rare (e.g., ε2/ε2 and ε4/ε4), the ApoE genotype odds ratios were calculated by collapsing patients into 2 main categories: those with at least 1 ε4 allele present and those with no ε4 allele. Crude odds ratios were calculated independently. Adjusted odds ratios were obtained by entering all significant variables and combination of interaction terms into a multivariate logistic regression model, followed by a backward conditional algorithm to assess for significance.

**Table 1: Distribution of changes in diagnosis among elderly subjects without dementia at phase 1 of study**

| Change in diagnosis between phase 1 and phase 2 | No. (and %) of subjects | Women | Men | All |
|-----------------------------------------------|--------------------------|-------|-----|-----|
| Normal → normal                               | 582 (39.6)               | 328 (38.5) | 254 (41.6) | 582 (39.6) |
| Normal → CIND                                 | 337 (22.9)               | 190 (22.0)  | 147 (24.2) | 337 (22.9) |
| Normal → AD                                   | 140 (9.5)                | 94 (10.9)    | 46 (7.6)     | 140 (9.5) |
| Normal → VaD                                  | 51 (3.5)                 | 27 (3.1)    | 24 (3.9)     | 51 (3.5)  |
| Normal → other dementia                       | 63 (4.3)                 | 41 (4.8)    | 22 (3.6)     | 63 (4.3)  |
| CIND → normal                                 | 29 (2.0)                 | 17 (1.9)    | 12 (1.9)     | 29 (2.0)  |
| CIND → CIND                                   | 85 (5.8)                 | 52 (6.0)    | 33 (5.4)     | 85 (5.8)  |
| CIND → AD                                     | 70 (4.8)                 | 50 (5.8)    | 20 (3.3)     | 70 (4.8)  |
| CIND → VaD                                    | 9 (0.6)                  | 7 (0.8)     | 2 (0.3)      | 9 (0.6)   |
| CIND → other dementia                         | 68 (4.6)                 | 43 (4.9)    | 25 (4.1)     | 68 (4.6)  |
| CIND → death or loss to follow-up             | 35 (2.4)                 | 13 (1.5)    | 22 (3.6)     | 35 (2.4)  |

Note: AD = Alzheimer’s disease, VaD = vascular dementia, CIND = “cognitive impairment no dementia.”

**Results**

The distribution of changes in diagnoses of all 1469 cases by sex are summarized in Table 1. As expected from the demographic distribution in the elderly population, there were more women than men. Two cases in each of the control group, the incident AD group and the CIND group were missing information on education level, and these cases were omitted from the subsequent logistic regression analyses and calculations of adjusted odds ratios (ORs). Overall, women were at a higher risk than men for any type of cognitive problems after adjustment for age and level of education (OR 1.28, p = 0.018).

The comparisons of age and education level across different diagnostic categories are shown in Fig. 1. There were significant differences in age between the control group (mean age 75.6), the group with CIND (mean age 77.8) and the group with AD (mean age 82.7) (Fig. 1A). Among patients whose CIND converted to another condition, those who converted to having AD (mean age 80.5) were significantly older than the control group, but they were not significantly younger or older than those within the CIND group (Fig. 1B). In the analysis of the effect of education, the control subjects (mean 10.4 years of education) had a significantly higher level of education than subjects with CIND (mean 9.2 years) and those with AD (mean 8.9 years) (Fig. 1C). The control group also had a significantly higher level of education than patients whose CIND converted to AD (mean 7.9 years), those whose CIND converted to VaD (mean 4.7 years) and those whose CIND remained the same (mean 7.8 years), but their education level did not differ significantly from that of subjects whose CIND converted back to normal (mean 9.0 years) (Fig. 1D).

The distribution of ApoE ε4 genotype in each diagnostic category is summarized in Table 2. As expected, the proportion of subjects with the ApoE ε4 genotype was significantly higher among patients with AD and VaD as well as among subjects whose CIND converted to AD (p < 0.001). In contrast, the proportion of patients with ApoE ε4 allele in the group with incident CIND and stable CIND and the group whose CIND converted to normal did not differ significantly from that of subjects whose CIND converted back to normal (mean 9.0 years) (Fig. 1D).

Since the effects of sex, age and years of education are known to be important risk factors for cognitive changes, these variables and ApoE ε4 status and their first order interaction terms were first analyzed independently (online Tables A and B, available at www.cmaj.ca/cgi/content/full/171/8/863/DC1); all significant factors were then analyzed together using multivariate logistic regression modelling (Tables 3 and 4). The presence of the ApoE ε4 allele, advanced age and being female were all significant risk factors for AD, and increased years of education was a protective factor. The presence of the ApoE ε4 allele was also a significant risk factor for VaD; however, it was not a significant risk factor for conversion from normal to CIND. For sub-
jects with CIND, the presence of the ApoE ε4 allele was a significant predictor for conversion to AD. There was a significant interaction effect of ApoE ε4 allele and age at onset of AD and for conversion from CIND to AD, which suggests that possession of an ApoE ε4 allele is associated with earlier age at onset of AD and earlier conversion from CIND to AD.

To examine the clinical utility of ApoE ε4 genotype as a predictor for conversion from CIND to AD, we calculated its sensitivity and specificity by comparing the outcome of subjects whose CIND converted to AD with the outcome of CIND subjects who were stable or reverted to normal. The sensitivity was 0.31 and specificity 0.79. When applied to this CIND population, it had a positive predictive value of 0.48 and a negative predictive value of 0.65. When applied to the general CSHA population (i.e., a community sample of elderly patients over age 65), it had a positive predictive value of 0.30 and a negative predictive value of 0.84.

**Interpretation**

The current study provides one of the largest population-based samples assembled for genetic association testing. We have shown that possession of the ApoE ε4 allele is an important predictor for conversion from CIND to AD. This raises the question of the clinical utility of ApoE ε4 genotyping as a diagnostic test or diagnostic adjunct in predicting the progression from CIND to AD. The relatively low predictive values in this study were likely due, in part, to the relatively high base rate of conversion from CIND to AD. Based on the sensitivity, specificity and predictive values, we would not recommend ApoE ε4 genotyping as a diagnostic test to predict conversion to AD from either normal or CIND status. However, this AD risk factor could have an important role in research studies. When used in conjunction with age to select subjects for a study of primary prevention of AD, a 75-year-old subject with an ε4 allele can be estimated to be about 25 times more likely than a 65-year-old non-ε4 carrier.
to have AD within 5 years. It should then be possible to use this information to optimize inclusion criteria for key clinical trials that are designed to delay the onset of AD in subjects without dementia. It may also allow recruitment of an enriched sample of subjects with CIND to test interventions designed to slow progression or delay conversion to AD.

In this study, the ApoE ε4 genotype was not significant in predicting incident CIND cases. This apparent discrepancy may be related to the conceptual basis of CIND and its diagnostic heterogeneity. The CIND diagnosis is deliberately broad and encompasses the full range of cognitive impairments in memory and learning and in perceptual-motor, linguistic and executive functioning that fall short of meeting clinically defined dementia. As such, the criteria include a wide range of medical, psychiatric and neurological disorders beyond pre-AD, which likely affects the conversion rate to CIND as a whole. The transition from normal to a more specified pre-AD subtype of CIND may be associated with the ApoE ε4 genotype. Our study design did not allow this to be reliably tested, since this type of subclassification would have been post hoc and hampered by very small samples.

Our data also confirmed that, for the Canadian population, the ApoE ε4 allele is a significant risk factor for AD as well as for VaD. Previous reports on an association between ApoE ε4 and VaD have been mixed. These inconsistencies may be a result of population stratification — subjects who differ in their ethnic background may possess different genetic susceptibility loci. Also, results of some of the smaller studies may be negative because of inadequate power. In addition, bias in selection of controls may lead to an incorrect measure of association. The CSHA study consists primarily of a white population because of the requirement that all subjects be fluent in English or French in order for neuropsychological testing to be interpreted properly. The ApoE allele frequency and genotype distributions of our CSHA control subjects are similar to those of other, more homogeneous elderly cohorts, which suggests that it is an appropriate group for comparison with other dementia subgroups.

**Table 2: Distribution of ApoE ε4 genotype among subjects with incident AD, VaD and CIND and among those with CIND conversion**

| Diagnosis                | ApoE ε4 genotype; no. (and %) of subjects |
|--------------------------|-------------------------------------------|
|                          | No ε4 | Hemizygous ε4 | Homozygous ε4 |
| Normal (n = 582)         | 467 (80.2) | 114 (19.6) | 1 (0.2) |
| Incident CIND (n = 337)  | 260 (77.2) | 73 (21.7) | 4 (1.2) |
| Incident AD (n = 140)    | 90 (64.3) | 46 (32.9) | 4 (2.9) |
| Incident VaD (n = 51)    | 29 (56.9) | 21 (41.2) | 1 (2.0) |
| CIND → normal (n = 29)   | 22 (75.9) | 5 (17.2) | 2 (6.9) |
| CIND → CIND (n = 85)     | 68 (80.0) | 17 (20.0) | 0 (0.0) |
| CIND → AD (n = 70)       | 48 (68.6) | 19 (27.1) | 3 (4.3) |
| CIND → VaD (n = 9)       | 7 (77.8) | 2 (22.2) | 0 (0.0) |

Note: ApoE = apolipoprotein E.

**Table 3: Adjusted odds ratios* for incident cases of CIND, AD and VaD**

| Diagnosis | Age (for every yr increase) | Sex (F:M) | Education (for every yr increase) | Presence v. absence of ApoE ε4 allele |
|-----------|-----------------------------|-----------|-----------------------------------|--------------------------------------|
| CIND (n = 335) | 1.04 (1.02–1.07) | NS | 0.91 (0.88–0.95) | NS |
| AD (n = 138)   | 1.12† (1.09–1.15) | 1.45 (1.01–2.10) | 0.88 (0.84–0.92) | 2.89† (1.96–4.28) |
| VaD (n = 51)   | NS | NS | 0.88 (0.82–0.95) | 3.13 (1.76–5.55) |

Note: CI = confidence interval, NS = not significant in crude odds ratio analyses.

*Adjusted odds ratios were calculated with all significant variables and interaction terms first entered into the logistic regression model and then removed with a backward conditional likelihood ratio algorithm.

†Significant interaction was found between the presence of ApoE ε4 allele and age, with the presence of the ε4 allele causing a decrease in age at onset of dementia. No significant first-degree interactions were found between other factors.

**Table 4: Adjusted odds ratios* for cases progressing from CIND**

| Progression   | Age (for every yr increase) | Sex (F:M) | Education (for every yr increase) | Presence v. absence of ApoE ε4 allele |
|---------------|-----------------------------|-----------|-----------------------------------|--------------------------------------|
| CIND → normal (n = 29) | NS | NS | NS | NS |
| CIND → CIND (n = 85)   | 1.05 (1.01–1.09) | NS | 0.83 (0.77–0.89) | NS |
| CIND → AD (n = 68)    | 1.13† (1.08–1.18) | 1.61 (0.90–2.89) | 0.82 (0.76–0.89) | 2.69† (1.48–4.92) |
| CIND → VaD (n = 9)    | 1.11 (1.01–1.23) | NS | 0.62 (0.49–0.79) | NS |

*Adjusted odds ratios were calculated with all significant variables and interaction terms first entered into the logistic regression model and then removed with a backward conditional likelihood ratio algorithm.

†Significant interaction was found between the presence of ApoE ε4 allele and age, with the presence of the ε4 allele causing a decrease in age at onset of dementia. No significant first-degree interactions were found between other factors.
Among the limitations of our study is the relatively older age of the study population. In trying to address the problem of cognitive impairment with aging, the CSHA deliberately over-sampled subjects over the age of 75, with a resultant high rate of loss to follow-up owing to high mortality. Subjects who were available for phase 2 of the study were likely healthier than the general population, since the study excluded many who died at an earlier age because of other illnesses. Since ApoE ε4 genotype is also a risk factor for cardiovascular disease, and there is also a significant interaction effect between age at onset of dementia and possession of an ApoE ε4 allele, the effect of ApoE ε4 genotype (and our odds ratios estimate) on the risk for AD in this population is likely to be lower than the effect in a younger population. This is also reflected on the overall rarity of homozygous ε4 allele in our sample. Another caveat around the VaD analyses is that neuroimaging was not required for the diagnosis of VaD, which may have led to under-recognition of VaD in the current study. Our finding that ApoE ε4 genotype, increasing age, female sex and lower level of education are all risk factors for incident AD is consistent with other studies, which provides some important external validity to our sample.

Despite these limitations, our study demonstrates a clear relation between ApoE ε4 genotype and the progression of CIND to dementia and underscores the importance of ApoE ε4 genotype in the pathogenesis in AD and VaD.

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