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How can elderly apolipoprotein E ε4 carriers remain free from dementia?

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Abstract

Apolipoprotein E (APOE) ε4 is a major risk factor for Alzheimer's disease (AD) and dementia, but not all ε4 carriers develop dementia. We sought to identify factors that may play a role in modifying the risk of dementia due to ε4. A cognitively intact cohort (n = 932, age ≥ 75) was followed for 9 years to detect incident dementia cases. At baseline, information on education, leisure activities, and vascular risk factors was collected, and APOE was genotyped. During the follow-up, 324 subjects developed dementia, including 247 AD cases. The hazard ratio (HR, 95% confidence interval [95% CI]) of dementia related to the ε4 was 1.39 (1.11–1.76), while the risk was reduced when ε4 carriers had high education, no vascular risk factors, or high score of leisure activities. Among ε4 carriers, the multiadjusted HRs of dementia that were associated with high education, high level of leisure activities, and absence of vascular risk factors were 0.59 (0.40–0.87), 0.49 (0.29–0.85), and 0.61 (0.41–0.90), respectively. The ε4 carriers with these factors had about 1.2 years delayed time to dementia onset compared with those without these factors. High education, active leisure activities, or maintaining vascular health seems to reduce the risk of dementia related to APOE ε4. The ε4 carriers with these characteristics appear to have similar dementia-free survival time to non-ε4 carriers.

Keywords: APOE ε4 allele; Alzheimer's disease; Dementia; Hazard ratio; Prospective cohort study; Education; Leisure activities; Vascular risk factors

1. Introduction

The apolipoprotein E (APOE) ε4 allele is a major susceptibility gene for late-onset Alzheimer's disease (AD) (Bertram et al., 2007). The proportion of patients with dementia that is attributable to the APOE ε4 is estimated to be 20% in people aged ≥ 55 years (Slooter et al., 1998) and 12.9% among people aged > 75 years (Guo et al., 2001) compared with the ε3/ε3 genotype. The ε4 allele has been associated with an earlier age at onset of AD with dosage effect according to the number of ε4 allele (Farrer et al., 1997), and is a risk factor for other types of dementia as well (Takeda et al., 2010). The APOE ε4 has been implicated as playing an unfavorable role in β-amyloid deposition, neuronal maintenances, neuronal signaling pathways, and cytoskeletal structure and function (Gee and Keller, 2005; Huang et al., 2004).

Although the ε4 allele increases the risk for developing dementia, carrying the allele does not necessarily lead to the disease, even when present in homozygosity (Laws et al., 2003). A considerable proportion of ε4 carriers do escape the disease (Khachaturian et al., 2004; Myers et al., 1996). In other words, not all individuals carrying the APOE ε4

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ultimately develop dementia, even over an extended lifespan, suggesting that environmental factors may modulate the effect of this allele on the risk of AD (Khachaturian et al., 2004). Indeed, evidence has shown that the regulation of the transcription of APOE can be influenced by nongenetic factors (Laws et al., 2003). Despite numerous longitudinal studies that have consistently shown a protective role of high education, leisure activities, and absence of vascular risk factors against dementia (Middleton and Yaffe, 2009), few studies have addressed the potential role of these factors in modifying the association between APOE ε4 and the risk of dementia. A longitudinal study has reported that high education may attenuate the risk effect of ε4 on dementia (Ngandu et al., 2007), which, however, can be aggravated by vascular diseases as shown in several studies (Hofman et al., 1997; Peila et al., 2001). Two studies that assessed the combined effect of physical activities and APOE ε4 on dementia risk have produced contradictory results (Podewils et al., 2005; Rovio et al., 2005).

We have previously reported the risk effect of APOE ε4 (Qiu et al., 2004) and the protective effect of high education (Qiu et al., 2001; Wang et al., 2012) and leisure activities (Karp et al., 2006; Wang et al., 2002) on the development of dementia and AD. In a series of studies from the Kungsholmen Project, we had identified that high systolic (Guo et al., 2001) and low diastolic blood pressure (Qiu et al., 2003), stroke (Zhu et al., 2000), and heart failure (Qiu et al., 2006), as well as diabetes (Xu et al., 2004) and prediabetes (Xu et al., 2007), were all related to an increased risk of dementia, AD, or both (Qiu et al., 2010; Xu et al., 2009). We hypothesized that high education, a high level of leisure activities, and absence of vascular risk factors may play a beneficial role in modifying the association of APOE ε4 with dementia and AD. The present study was intended to verify this hypothesis by examining the combined effect of APOE ε4 with these factors on the risk of dementia and AD using 9-year follow-up data from the Kungsholmen project.

2. Methods

2.1. Study population

The study population was derived from the Kungsholmen Project, a population-based cohort study on aging and dementia, which has been fully described elsewhere (Fratiglioni et al., 1992b, 1997). Briefly, all registered inhabitants who were living in the Kungsholmen district of Stockholm, Sweden, and who were aged ≥ 75 years in October 1987 were initially invited to participate in the project. At baseline, 225 of the 1700 participants were diagnosed with dementia following the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria (American Psychiatric Association, 1987) with a 2-phase survey. Of the remaining 1475 dementia-free persons, 172 refused to participate in the first follow-up or had moved, 316 had no blood sample available for genotyping, and 55 with Mini-Mental State Examination (MMSE) scores < 24 were excluded, leaving 932 subjects for the current analysis.

During the 9-year follow-up, three waves of clinical examination were carried out, each with an average interval of 3 years. Throughout the whole follow-up period, 346 subjects died and 51 refused participation. Medical records and death certificates were available for deceased subjects.

Informed consent was obtained for all participants, with informants providing consent for cognitively impaired persons. The ethics committee at the Karolinska Institutet, Stockholm, approved all phases of the Kungsholmen Project.

2.2. Baseline data collection

Data on demographic features (i.e., age, sex, and education) were collected from the subjects following standardized protocols (Fratiglioni et al., 1992b, 1997). Education was measured as the maximum years of formal schooling and was dichotomized into 2 categories: elementary school (< 8 years of schooling and/or vocational training) and high school or university (≥ 8 years), based on a previous study (Qiu et al., 2001). Information on leisure activities was obtained from the subjects by means of a personal interview carried out by trained nurses at baseline with open questions. Subjects were asked whether they regularly engaged in any particular activities, the type of activities, and frequency of participation. The reported leisure activities were grouped into 29 main types of activities. A mental, social, and physical component score was assigned to each of the 29 activities. The grading of the three components was coded as follows: 0 = none, 1 = low, 2 = moderate, 3 = high. The rated scores were added to a sum of scores for each person and each component across the range of activities (Karp et al., 2006). Further, the mental (range: 0–18), social (range: 0–13), and physical component scores (range: 0–12) were dichotomized according to the median values as low vs. high (i.e., 0–3 vs. 4–18 for mental; 0 vs. 1–12 for physical, and 0–1 vs. 2–13 for social components), respectively. The assessment of leisure activities was validated previously (Karp et al., 2006). In this study, we grouped the three components in a single variable called "leisure activity" with three categories as "high in all three components," "high in one or two components," and "low in all three components."

Based on our previous findings, vascular risk factors included vascular disorders (high systolic and low diastolic pressure, stroke, and heart failure), diabetes, and prediabetes. Body mass index (BMI), as a potential confounder, was calculated as measured weight (kg) divided by height (meters) squared. Arterial blood pressure (i.e., systolic Korotkoff phase I and diastolic phase V) was measured by nurses after the subjects rested in a seated position for at least 5 minutes. High blood pressure was defined as systolic pressure > 180 mm Hg and low blood pressure as diastolic