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APOE ε4 Genotype and the Risk of Subjective Cognitive Impairment in Elderly Persons

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Abstract

We compared the risk of subjective cognitive impairment (SCI) between cases (APOE ε4 carriers) and controls (APOE ε4 non-carriers. SCI was assessed by a validated self-reported questionnaire. We used multi variable logistic regression analyses to compute odds ratios (95% confidence intervals) adjusted for age, sex, education, and marital status. Data were available on 114 participants (83 women; 47 APOE ε4 carriers; mean age 69 years). The risk of SCI was significantly higher among cases than controls, particularly for those aged 70 years and older. Our findings should be considered preliminary until confirmed by a prospective cohort study.

Keywords

subjective cognitive impairment; APOE ε4; mild cognitive impairment; dementia

There is a growing interest in the identification of the presymptomatic phase of Alzheimer's disease (AD).[1, 2] One construct that refers to the incipient stage of AD and may constitute a high-risk state for dementia is subjective cognitive impairment (SCI).[3] SCI is defined as a subjective memory or cognitive complaint that is not corroborated by psychometric or mental status tests.[4, 5] However, emerging data indicate that subtle neuropsychological abnormalities can occur in persons with subjective memory complaint.[6, 7] The description of SCI was derived from studies that employed the Global Deterioration Scale (GDS) to define cognitive and functional status between normal aging and dementia.[8] The GDS classifies persons on an ordinal scale spanning from GDS 1–7. Reisberg proposed six criteria for primary idiopathic SCI including (1) subjective cognitive deficits, (2) the subject believes that he or she has experienced a decline in cognitive function compared to previous years, (3) no medical, neurologic, or psychiatric conditions that can account for the subjective cognitive complaint, (4) no overt cognitive deficits which might be elicited in the context of

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a detailed clinical interview or might be evident to a knowledgeable informant, (5) normal cognitive performance on objective testing, and (6) no dementia.[4]

In the past, memory complaint or SCI was generally assumed to be a manifestation of depression; however, this assertion did not stand empirical scrutiny as investigators have reported that SCI cannot be attributed to a psychiatric condition.[5, 9] Furthermore, emerging data indicate that SCI is associated with both chemical[10] and neuroimaging biomarkers of AD.[11–13]

Apolipoprotein E ε4 is a well-known risk factor for sporadic and familial late-onset Alzheimer's disease.[14–16] It is also a risk factor for mild cognitive impairment (MCI) due to AD.[17, 18] APOE ε4 is a prognostic factor for the clinical progression of AD.[19, 20] However, it remains unclear if APOE ε4 is also a risk factor for SCI. Few studies have examined the association between the construct of "memory complaints" and APOE ε4[21–25]; whereas we used Reisberg's definition of SCI in order to investigate SCI's association with APOE ε4 genotype.

Thus, the objective of our study was to examine the association between APOE ε4 genotype and subjective cognitive impairment, as defined by the Reisberg criteria, among participants that are classified as cognitively normal by an expert consensus panel after reviewing data from the neurological examination and objective neuropsychological tests.[26]

METHODS

Design, Setting, Study Sample

This case-control study was derived from the Arizona APOE cohort study which is conducted at the Mayo Clinic in Scottsdale, Arizona.[26] From January 1, 1994 through August 6, 2007, cognitively normal residents of Maricopa County aged 21 years and older were recruited through local media advertisements. Eligible participants for the current analyses were all cognitively normal persons on whom APOE ε4 data were available. Participants with MCI or dementia were excluded. All cognitively normal persons who are APOE ε4 carriers were classified as cases, whereas all cognitively normal persons who are not carriers of the APOE ε4 allele were classified as controls. Written informed consent was obtained from all study participants. The study was conducted with the approval of the institutional review board of the Mayo Clinic in Scottsdale, Arizona.

Assessment of Subjective Cognitive Impairment

Study participants completed a validated, self-reported Memory Frequency Questionnaire (MFQ).[27, 28] The MFQ has 64 items with ordinal responses ranging from 1 (extreme difficulty with a memory item) to 7 (no difficulty at all with a memory item). The questionnaire assesses the ability to recall names (language), recognize familiar faces, directions to places, recall events within the past several months to years etc. The first question of the MFQ is the main item and inquires about memory as follows: "How would you rate your memory in terms of the kinds of problems that you have? Rate the problem from 1 (major problems) to 7 (no problems) with 4 being related to minor problems". A cognitively normal person, as defined by a normal neurological examination and

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neuropsychological tests[26] and who also scored less than 7 points on this main item was classified in the SCI category.

Measurement of APOE Genotype

After obtaining informed consent, blood was drawn from the study participants. APOE ε4 genotypes were determined from DNA using a polymerase chain reaction amplification.[29] Cases and controls were not aware of their APOE ε4 status.

Neuropsychological Tests

The study participants underwent the following evaluations: acquisition of medical history, neurological examination, and a structured psychiatric interview. The tests administered include the Folstein Mini-Mental State Exam (MMSE),[30, 31] the Hamilton Depression Rating Scale (Ham-D),[32] a Functional Activities Questionnaire (FAQ),[33] and Instrumental Activities of Daily Living Questionnaire (IADL).[34] Neuropsychological testing was performed to assess four cognitive domains (memory, executive functions, language, and spatial skills). The standardized battery of neuropsychological tests included the long-term memory score on the Auditory Verbal Learning Test (AVLT-LTM),[35] the Controlled Oral Word Association Test (COWAT) for evaluation of executive and language skills,[36] and the Judgment of Line Orientation (JLO) test for evaluation of visuospatial function.[36] Relevant information was provided by the participants as well as an informant who was usually the spouse. The entry criteria for this study included a score ≥ 27 on the MMSE (and a score of at ≥ 1 out of 3 on the recall subtest), a score of ≤ 10 on the Ham-D rating scale, and normal function according to the FAQ and the IADL scale.[26] A consensus panel of behavioral neurologists determined the cognitive status of each participant after reviewing neurological and neuropsychological data, and based on published criteria of MCI [18, 37] and DSM-IV criteria for dementia. A description of the neuropsychological and behavioral tests that were administered to the participants of the APOE cohort study is also provided elsewhere.[26]

Statistical Analysis

We used two-sample *t* tests to compare means of continuous variables, and percentages were compared by using the Pearson chi-square test. We conducted a multi-variable logistic regression analysis in order to calculate odds ratios (OR) and 95% confidence intervals (95% CI) after adjusting for age, sex, education, and marital status. We then used the OR (95% CI) to compare the "risk" of SCI between the two groups (cognitively normal participants who are APOE ε4 carriers versus non-carriers). Statistical testing was performed at the conventional two-tailed alpha level of 0.05. Analyses were conducted using SAS® software (Cary, NC, USA).

RESULTS

Demographics

There were 114 cognitively normal persons for whom relevant data from the MFQ were available. The participants ranged in age from 24–91 years with a mean (SD) of 69.1 (9.5) years. With regard to the frequency and distribution of APOE genotypes, 6 participants were APOE ε2/ε3 carriers, 61 participants were APOE ε3/ε3 carriers, and 47 participants (41%)

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carried APOE ε4 allele. Of these 47 APOE ε4 carriers, 3 persons had APOE ε2/ε4, 38 persons had APOE ε3/ε4, and 6 had APOE ε4/ε4. There were no group differences (APOE ε4 carrier versus non-carrier) in age, sex, and marital status. Where there is a group difference (education), adjusting for it by analysis did not appreciably alter the OR (Tables 1 and 2).

Key Findings

SCI was common among both cases and controls, i.e., 43/46 (93%) APOE ε4 carriers and 52/65 (80%) non-carriers reported SCI as defined by a score <7 on the main item of the MFQ (OR: 3.6, 95% CI: 0.96–13). Adjusting for age, sex, education level and marital status slightly reduced the OR to 3.2 (95% CI: 0.82–12). All but one (83%) of the six APOE ε4 homozygotes reported SCI. When comparing only cases and controls above the age of 70 years, 23/23 (100%) APOE ε4 carriers and 23/30 (77%) non-carriers reported SCI (Table 3). The odds of having SCI were significantly higher among carriers than among non-carriers (OR approaches ∞; p=0.02) in this age group. No significant difference was observed in the frequency of SCI between carriers (20/23; 87%) and non-carriers (29/35; 83%) aged ≤70 years (OR: 1.38, 95% CI: 0.31–6.2).

DISCUSSION

Here we report that the odds of having SCI are dependent on APOE ε4 carrier status and age such that cognitively normal individuals who are APOE ε4 carriers and are above the age of 70 years have increased odds of having SCI. The odds of having SCI are not increased in persons who are aged 70 years and younger even if they are APOE ε4 carriers.

APOE ε4 is a risk factor for AD and MCI; however, it is unknown if it is also a risk factor for SCI. Furthermore, we conducted a stratified analysis by age group in order to investigate if SCI is dependent on both APOE ε4 and age. The relations between APOE ε4 and similar constructs such as “subjective memory complaint” or “subjective memory impairment” have been reported. Even though these constructs may not be identical with SCI, the results of those studies are still important contributions to the field of SCI.

Consistent with our findings, Chinese investigators recently reported a slightly higher frequency of the APOE ε4 allele in 17 individuals with SCI compared to 75 normal controls.[38] Similarly, researchers from Spain observed a higher frequency of APOE ε4 allele in 27 persons with memory complaints without dementia compared to 35 healthy controls.[21] Additionally, a multi-centered study that involved a sample of 39 cognitively normal persons aged 50–82 years reported that participants who were APOE ε4 carriers (N=19) had an increased subjective memory impairment compared to non-carriers (N=20).[23] A group of Australian, American, and German researchers conducted a study to investigate the difference in APOE ε4 genotype between 98 elderly individuals with memory complaints and 49 controls . They also found that persons with subjective memory complaints exhibited a significantly higher frequency of the APOE ε4 allele compared to the controls.[22] Investigators from the “Longitudinal Aging Study Amsterdam” reported a slightly, but not significantly, higher proportion of APOE ε4 carriers among participants who expressed memory complaints.[25]

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Discrepant findings of no association between APOE ε4 and memory complaints have also been reported. For example, investigators from the University of California-Los Angeles and University of Miami did not observe an association between APOE ε4 genotype and subjective memory complaints as assessed by using a Memory Questionnaire in a sample of 232 older adults who were aged 60 years or older.[24] The discrepancy between their observations and our finding may be due to methodological differences. Importantly, it should be noted that the Harwood et al. study included participants with the age of 60 years and older, whereas our study demonstrates that the association between APOE ε4 carrier status and SCI was evident only in participants over the age of 70 years. Thus, it is tempting to speculate that the results of the Harwood et al. study might have yielded associations between the variables if age had been stratified differently.

The strength of our study is that participants were recruited from the Arizona APOE cohort, where participants undergo extensive and detailed evaluations pertaining to neurological, psychiatric and cognitive variables. The limitation of our study pertains to the study design. Case-control studies can be used to test hypotheses. However, causal inference is stronger when case-control findings are confirmed in a prospective cohort study. We further assessed subjective cognitive impairment based on a self-reported, validated questionnaire. Recall bias may therefore be present in this study. Our findings should thus be considered as preliminary until they are confirmed in a prospective cohort study with a larger sample size.

CONCLUSIONS

We observed that the odds of having subjective cognitive impairment are higher in cognitively normal individuals who are APOE ε4 carriers and who are also above the age of 70 years. This finding contributes to the growing body of research which identifies APOE ε4 as an important risk factor of cognitive decline and Alzheimer's disease. Further research, especially population-based prospective cohort studies, is needed to confirm these findings.

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TABLE 1

Demographic Characteristics of the Cases and Controls

Variable	APOE ε4 Carrier (N=47)	APOE ε4 Non-carrier (N=67)	OR	95% CI	p
Age, >70 years	24 (51%)	32 (48%)	1.14	0.54–2.40	0.73
Female	32 (68%)	51 (76%)	0.67	0.29–1.54	0.34
Married	35 (74%)	40 (60%)	1.97	0.87–4.50	0.10
Education, >16 years	24 (51%)	28 (42%)	1.45	0.69–3.10	0.33

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TABLE 2

Demographic Characteristics of the Cases and Controls

Variable	APOE ε4 Carrier (N=47)	APOE ε4 Non-carrier (N=67)	p
Age[a] (Mean [SD])	69.7 (9.4)	68.7 (9.6)	0.60
Female	32 (68%)	51 (76%)	0.34
Married	35 (74%)	40 (60%)	0.10
Education[b] (Mean [SD])	17.0 (2.3)	16.0 (2.5)	0.04

[a] Age is given in years.

[b] Education is given in years.

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TABLE 3

Stratified Analysis by Age (>70 versus ≤70 years old)[a]

VARIABLE	APOE ε4 Carrier	APOE ε4 Non-carrier	OR	95% CI	p
All	43/46 (93%)	52/65 (80%)	3.6	0.96–13	0.046
Age, >70 years	23/23 (100%)	23/30 (77%)	*b*		0.02
Age, ≤70 years	20/23 (87%)	29/35 (83%)	1.38	0.31–6.2	>0.99

[a]Three participants (1 APOE ε4 carrier, 2 APOE ε4 non-carriers) had a missing value for the Memory Frequency Questionnaire main item. Those three participants had complete data for the remaining items on the Memory Frequency Questionnaire.

[b]OR approaches infinity.