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Early-Onset and Late-Onset Depression Are Independent of the Genetic Polymorphism of Apolipoprotein E

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Key Words

Apolipoprotein E · Polymorphism · Depression · Early-onset · Late-onset · Alzheimer's disease · Association · Survival analysis

Abstract

The recently shown association between apolipoprotein E (APOE) genotype and depressive illness has been challenged by subsequent studies. However, controversial results may derive from the different diagnostic criteria used for depression and from the small numbers of depressed patients included in the studies. We examined the association between depression and the genetic polymorphism of APOE in a large sample of depressed patients, Alzheimer's disease (AD) patients, and healthy controls following clear definitions for late-life depression. The cumulative incidence of depression depending on the age at onset of the first episode was examined by survival analysis. Our data do not disconfirm the hypothesis of depression sharing some common pathophysiologic features with AD, however, it seems very unlikely that the APOE genotype will elucidate the assumed common mechanisms.

Introduction

The finding that the frequency of the apolipoprotein E ε4 (APOE ε4) allele is increased in Alzheimer's disease (AD) [1] has led to numerous studies examining the allelic distribution of APOE ε4 in other disorders, which share common clinical and, presumably, aetiological characteristics with AD. Depression is often accompanied by cognitive deficits similar to those occurring in AD [2] and has been discussed as a possible risk factor for developing AD [3]. Moreover, there seems to be a significant comorbidity between depression and AD [4]. The increased frequency of the APOE ε3/ε4 genotype in non-demented, late-onset depressed patients [5] gave rise to the hypothesis that late-onset depression (LOD) shares at least some common pathophysiological mechanisms with AD. The observation that LOD is a risk factor for developing AD [6] and that patients with AD and the APOE ε3/ε4 genotype show increased depressive manifestations [7] seemed to strengthen this hypothesis. However, other studies failed to replicate a significant association between depression and the genetic polymorphism of APOE [8–14] or showed increased APOE ε4 allele frequency in a small subgroup of elderly depressed patients with psychotic symptoms [15]. It is hitherto difficult to draw a final conclusion from the results of these studies, because they only allow limited

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Table 1. APOE genotype and APOE ε4 allele distribution in healthy controls, patients with EOD, patients with LOD and AD patients

	Healthy controls (n = 191)	EOD patients (n = 129)	LOD patients (n = 31)	AD patients (n = 102)
APOE genotype[a]				
ε3ε3	109 (57.1%)	70 (54.3%)	18 (58.1%)	31 (30.4%)
ε2ε3	33 (17.3%)	20 (15.5%)	5 (16.1%)	9 (8.9%)
ε3ε4	46 (24.1%)	30 (23.3%)	7 (22.6%)	40 (39.2%)
ε4ε4	1 (0.5%)	6 (4.6%)	–	19 (18.6%)
ε2ε4	2 (1.0%)	3 (2.3%)	1 (3.2%)	3 (2.9%)
APOE ε4 allele frequency[b]				
No ε4	86.9%	82.6%	87.1%	60.3%
ε4 present	13.1%	17.4%	12.9%	39.7%

[a] For the entire group: $\chi^2 = 63.2$, d.f. = 12, $p < 0.0001$.
[b] χ^2 test between healthy controls, EOD, and LOD patients: $\chi^2 = 2.5$, d.f. = 2, $p = 0.29$.
χ^2 test between healthy controls and LOD patients: $\chi^2 = 0.02$, d.f. = 1, $p > 0.5$.
χ^2 test between EOD and LOD patients: $\chi^2 = 0.5$, d.f. = 1, $p = 0.5$.
All comparisons were corrected for multiple testing.

comparison: (a) the positive association between APOE genotype and depression was based on an insufficient number of depressed patients (12 early-onset depressed and 30 late-onset depressed patients) [5], (b) the definition of the age at onset for late-life depression varies (i.e. >45, 60, or 65 years) [5, 10, 14], (c) some authors use the term depressive illness after development of AD [8], and (d) other authors define depressive episodes in elderly patients as geriatric depression, even though they suffered from recurrent depression which first appeared in their 30s [15].

These apparent controversies led us to examine the association between depression and the genetic polymorphism of APOE in a large sample of depressed patients, AD patients, and healthy controls following clear definitions for late-life depression. In order to exclude the possibility that the arbitrary subdivision of depression into an early-onset and a late-onset form confounded our analysis, we further examined the cumulative incidence of depression depending on the age at onset of the first episode using survival analysis.

Material and Methods

German AD patients (n = 102) with a mean age of 74.4 ± 10.3 years (range 51–101 years) were recruited from the out-patient memory disorders clinic of the Psychiatric Department of the University of Bonn; there were 68 (66.7%) females. The diagnosis of probable AD was performed by standard clinical evaluation according to NINCDS-ADRDA criteria [16]. Medical and family history, general medical and neurological examination, psychiatric interview, neuropsychological testing, blood and CSF studies, and CT scans were carried out to exclude other forms of dementia. Depressed patients (n = 160) were consecutively recruited in the Departement of Psychiatry, University of Bonn. The mean age was 68.0 ± 7.7 years (range:50–88 years). There were 105 female patients (65.6%). Non-demented, depressed patients underwent the same clinical evaluation as the AD group. The diagnosis of depression was made by 2 independent experienced psychiatrists. Patients with LOD (n = 31) were subjects 60 years of age or above at the first occurrence of a depressive episode (mean age: 70.2 ± 6.6 years, range: 61–86 years). Patients with other psychiatric disorders (e.g. schizophrenia, schizoaffective disorder, bipolar disorder) were not included. With the support of the local Census Bureau and the regional Board of Data Protection (Nordrhein-Westfalen, Germany) a stratified random sample of subjects aged over 50 years was selected from the elderly general population. The control group comprised 191 healthy subjects (92 males, 99 females) with a mean age of 70.6 ± 11.4 years (range 50–100 years). CT scans and liquor studies were not performed in the healthy subjects from the general population. In this group, exclusion of psychiatric disorders and dementia was made after an extensive psychiatric interview and neuropsychological testing. All patients and control subjects gave informed consent to participate in the study.

Leukocyte DNA was isolated following standard protocols. APOE genotyping was performed as described before [17]. APOE genotypes included ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4. The genotype ε2/ε2 was not observed. Genotyping was performed blind to clinical diagnosis. Frequencies were compared with the χ^2 test. Survival analysis was performed using the Kaplan-Meier method and the log rank statistics.

Results

Table 1 presents the distribution of the APOE genotypes and the frequency of the APOE ε4 allele in healthy controls, patients with early-onset depression (EOD), pa-

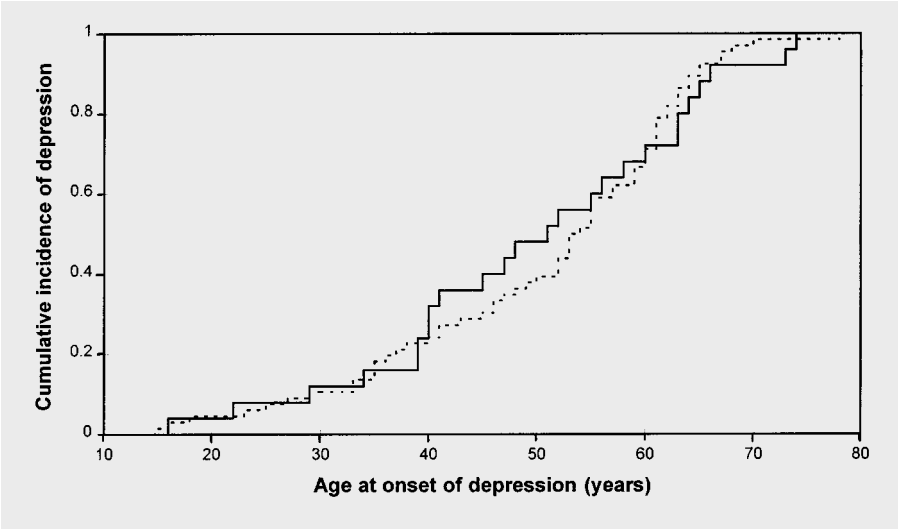

Fig. 1. Cumulative incidence of depression in non-demented, depressed patients with no (– – –) or those with at least one copy (——) of the APOE ε4 allele.

tients with LOD and AD patients. The significant overrepresentation of the ε3/ε4 genotype and the ε4/ε4 genotype in AD patients led to a very high χ^2 value when the entire group was tested ($\chi^2 = 63.2$, d.f. = 12, $p < 0.0001$). However, comparison of the APOE ε4 allele frequency in healthy controls, EOD patients, and LOD patients revealed no significant difference between these groups ($\chi^2 = 2.5$, d.f. = 2, $p = 0.29$). This applied also to pairwise comparisons between EOD and LOD patients ($\chi^2 = 0.5$, d.f. = 1, $p = 0.5$) and between healthy controls and LOD patients ($\chi^2 = 0.02$, d.f. = 1, $p > 0.5$).

Figure 1 shows the cumulative incidence of depression depending on the age at onset for non-demented, depressed patients with no or those with at least one copy of the APOE ε4 allele. There was no significant difference between the corresponding Kaplan-Meier curves (log rank statistics = 0.4, d.f. = 1, $p = 0.8$).

Discussion

The assumption that depressive illness and AD are distinct syndromes which may share common biological components [18] has recently found support by the finding that depressed AD patients show increased familial liability for depression that is independent of any familial liability for dementia [19]. Despite the absence of corresponding histopathological or experimental data, the observed increased frequency of the APOE ε3/ε4 genotype in non-demented, late-onset depressed patients [5] provided a missing link in the pathogenesis of AD and depression, although this observation was challenged by subsequent studies in elderly depressed patients [9, 10, 14, 15]. However, comparison of these studies is hampered by the fact that different definitions for the diagnosis of late-life depression were used, and that the number of depressed subjects was insufficient in many studies.

In the present study we used a large sample of healthy controls, depressed patients, and AD patients, and defined late-life depression in accordance with most authors [20–22]. We could not replicate the finding by Krishnan et al. [5], since there was no difference in the distribution of the APOE genotype in healthy controls and patients with LOD and EOD. The APOE allele frequencies were in almost perfect agreement with other studies [10]. Moreover, the performed survival analysis showed that the APOE ε4 allele has no influence on the age at onset of depression. The hypothesis of depression sharing some common pathophysiologic features with AD is not excluded by this data, however, it seems very unlikely that the APOE genotype will elucidate the assumed common mechanisms.

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