Association between the *APOE* genotype and psychopathologic symptoms in Alzheimer's disease

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Abstract

Background—Psychiatric symptoms occur frequently in the course of AD, are a frequent contributor to institutionalization, predict cognitive decline and death, and often require treatment with psychotropic medications. Previous studies investigating the association between *APOE* genotype and psychiatric symptomatology in AD have reported contradictory results.

Objective—To determine whether *APOE* genotype predicts incident psychiatric symptomatology in patients with AD.

Methods—Eighty-seven patients with AD at early stages and no psychiatric history were followed semiannually for up to 9.3 years (mean 5.5 years) for development of delusions, illusions, hallucinations, behavioral symptoms, and depression. Cox proportional hazards models were used to examine the relative risk for incident psychiatric symptomatology (outcome) in relation to *APOE* genotype (predictor).

Results—The presence of one ε4 allele carried a 2.5-fold risk, whereas the presence of two ε4 alleles carried a 5.6-fold risk for development of delusions. The associations remained significant even when age, ethnicity, sex, education, duration of disease, and cognitive and functional performance were controlled for. The presence of two ε4 alleles was associated with reduced risk for developing hallucinations in the adjusted analysis only. No significant associations were detected between *APOE* genotype and the incidence of illusions, behavioral symptoms, or depression.

Conclusion—The presence of one or more ε4 alleles is a significant predictor for the incidence of delusions in the course of AD.

Psychiatric symptoms occur frequently in the course of AD. The prevalence of delusions over the course of the illness is estimated at up to 75%,[1] of hallucinations to 50%,[1] and of psychotic symptoms in general to 75%.[1] Behavioral disturbances like wandering, agitation, or physical aggression have been noted in 52% to 71%,[2] whereas mood disorders in general

are also commonly seen, with frequencies of 27% to 69%.[2,3] Major depression, in particular, may be seen in up to 30% of patients with AD.[2,3]

Psychiatric symptoms are a major cause of anxiety and concern to both patients and caregivers and a frequent contributor to institutionalization.[4,5] They often require treatment with psychotropic medications, the use of which is associated with increased side effects in the elderly.[6] In addition, the presence of psychiatric symptoms in AD has been shown to be a predictor of faster cognitive decline and death.[7-9]

Some investigators have reported significant associations between *APOE* genotype and various psychiatric symptoms.[3,10-15] However, the majority of studies failed to demonstrate a significant relation.[16-27] All these studies were cross-sectional. The emergence of specific psychiatric manifestations is associated with the severity of cognitive impairment,[2,20] which in turn is largely a reflection of duration of illness. Psychotic symptoms, agitation, and aggression are considered to be uncommon in the early stages of the disease and become more frequent as the disease progresses.[2,20,28] Therefore, examining only the prevalence of these symptoms without taking into account "how far" the patient is into the disease course is an important limitation of previous studies. The use of patients with AD with variable duration of illness (and therefore of different stages of the disease) in previous cross-sectional studies has provided useful information but has not accurately recorded the time to development of psychiatric symptomatology.

We assessed the presence and nature of psychopathologic features every 6 months in a prospectively followed cohort of patients with early possible and probable AD. We determined whether *APOE* geno-type was associated with differential risk for development of these psychiatric manifestations.

Methods

Subjects

Subjects were drawn from the Predictors Study.[29,30] Patients met *Diagnostic and Statistical Manual (3rd rev. ed.)* criteria for primary degenerative dementia of the Alzheimer type[31] and National Institute of Neurologic Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.[32] Enrollment required a modified Mini-Mental State Examination (mMMSE) score of ≥30 (maximum mMMSE score, 57), which is approximately equivalent to a score of ≥16 on the original MMSE.[33-35]

For the purposes of the present analyses, we excluded patients with any history of either psychiatric hospitalization or use of medications for psychiatric problems at any time before the first evaluation. Although elimination of patients with AD based on premorbid psychiatric history might result in a subset of patients with lower frequency of depression that emerges after the onset of AD,[36] it simultaneously served the purpose of excluding subjects with psychopathologic symptoms emerging after the onset of AD. The resulting psychiatric symptom-free population was appropriate for evaluation not only of the frequency but also of the time until occurrence of incident psychiatric symptomatology (as required by survival analyses models).

Evaluation

At the initial visit, various demographic (age, ethnicity, sex, education, and so on) and disease severity features were assessed. Duration of illness as estimated by the clinician based on interviews with the patient and the informant was also recorded. The clinicians determined whether the patient was ever hospitalized or medications ever prescribed for psychiatric problems. Neurologic, psychiatric, and mental status examinations were

conducted at study entry and at 6-month intervals thereafter. Cognitive function was examined using the mMMSE.[33-35] Functional capacity was assessed using the Blessed Dementia Rating Scale (BDRS).[37]

APOE—*APOE* studies were not an original component of the Predictors Study (because when data collection was initiated, *APOE* testing was not available), but beginning in the sixth year of the study, available subjects were approached to contribute blood samples for analyses. The pattern of each subject's *APOE* isoforms was determined using the method of Hixson and Powers.[38] In brief, white blood cells were isolated from fresh blood samples after centrifugation at 2,000 rpm for 20 minutes at 4 °C, and DNA was prepared. The DNA was amplified by PCR using *APOE*-specific oligonucleotide primers and Taq polymerase. The *APOE* PCR products were then digested with 5 units of *Hha*I enzyme at 37 °C for 4 hours. The digest was electrophoresed on a 12% nondenaturing polyacrylamide gel for 3 hours at a constant current of 10 mA. The gels were treated with ethidium bromide for 10 to 15 minutes, and the DNA fragments were visualized by ultraviolet illumination. Fragments of DNA of known size were used as markers.

For the purpose of the analysis, patients were categorized into three groups: those with two ε4 alleles (ε4/ε4), those with one (ε3/ε4 or ε2/ε4), and those without any (ε3/ε3 or ε2/ε2 or ε3/ε2). The resulting three-level categorical variable was introduced as the predictor variable in Cox proportional hazards models, with the group without any ε4 allele being considered the reference.

Outcomes—The following outcomes were considered. A trained research technician administered the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)[39] to the informant at the initial examination and at 6-month intervals thereafter. The bulk of informants were spouses (70.1%) or adult children (21.8%). The informant rarely changed during follow-up. Inter-rater reliability for the major psychiatric symptom categories between the principal scale developer and a research technician (trained by the principal scale developer), whether concurrently rating a single interview ($k = 0.74$ to 1.00) or conducting separate interviews ($k = 0.53$ to 0.73), has been reported.[39]

Most CUSPAD items are scored dichotomously (i.e., present or absent). For delusions, the categories were general (strange ideas or unusual beliefs), paranoid (people are stealing things, or unfaithful wife/husband, or unfounded suspicions), abandonment (accused caregiver of plotting to leave him/her), somatic (false belief that the patient has cancer or other physical illness), misidentification (false belief that people are in the house when nobody is there, or that someone else is in the mirror, or that spouse/caregiver is an impostor, or that the patient's house is not his/her home, or that the characters on television are real), and a miscellaneous category. A patient was considered to have delusions if he or she had at least one of the above types of delusions. Hallucinations (auditory, visual, tactile, and olfactory) and illusions were also recorded. Patients were considered to have hallucinations if they had hallucinations in any of the four sensory modalities.

The items for depression were depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping, and change in appetite. Depression was considered in two different ways. Initially, patients were considered depressed if they had depressed mood only, regardless of responses on the sleep and appetite items. The analyses were repeated using as the definition of depression either depressed mood and difficulty sleeping or depressed mood and appetite changes. Because the results were similar, the analyses reported use of the first definition of depression.

The five items for behavioral disturbance were wandering away from home, verbal outbursts, physical threats or violence, agitation or restlessness, and sundowning (more confusion at night or during the evening compared with daytime). If a patient manifested any of the five behavioral disturbances, he or she was considered to have behavioral symptoms.

Statistical analysis

The χ^2 test and analysis of variance were used to examine associations between the *APOE* genotype and demographic characteristics or clinical features.

Cox proportional hazards analyses[40] used *APOE* geno-type as the predictor variable and the psychiatric symptoms as the outcome variables. Duration (in years) between the initial visit and either development of psychiatric symptoms or last evaluation without psychiatric symptoms was used as the timing variable. Patients with the outcome psychiatric symptoms at first evaluation were not included in the Cox analyses. Initial Cox models considered only the association between *APOE* and the incidence of psychiatric symptoms. In subsequent analyses, age, ethnicity, sex, education, disease duration, mMMSE score, and BDRS score (as recorded at initial evaluation) were introduced as covariates.

Results

Demographic/clinical features and APOE

Of the 252 patients with AD in the Predictors Study, 50 had history of either hospitalization for psychiatric reasons or treatment with medications for psychiatric reasons, and 4 subjects were missing these data. These patients were excluded from subsequent analyses. The subjects were followed for up to 9.3 years (mean 5.5 years, SD 2.3 years).

APOE genotypes were available for 87 of the remaining 198 subjects. *APOE* genotype distribution was as follows: ε4/ε4, 13 (14.9%); ε4/ε3, 32 (36.8%); ε4/ε2, 3 (3.4%); ε3/ε2, 5 (5.7%); and ε3/ε3, 34 (39.1%) (a distribution similar to that in other series of AD populations).[41,42] Those subjects for whom *APOE* genotype was not available, in comparison with those included in this study for whom *APOE* was available, were more likely to be female (65.2% compared with 34.8%; $p \leq 0.002$) and were more likely to manifest behavioral symptomatology (53.3% compared with 46.7%; $p \leq 0.012$). The two groups did not differ significantly in ethnic distribution, mean age, mean duration of disease, mean education, mean mMMSE scores at initial evaluation, mean BDRS scores at initial evaluation, or manifestation of any other psychiatric symptomatology.

Demographic, neuropsychologic, and clinical information at first evaluation as well as *APOE* genotype grouping according to number of ε4 alleles are presented in table 1. Sex ($p \leq 0.79$), age ($p \leq 0.87$), duration of disease ($p \leq 0.91$), years of education ($p \leq 0.92$), mMMSE score ($p \leq 0.18$), and BDRS score ($p \leq 0.10$) were similar across the subject groups with two or one or no ε4 allele. Because 89.7% of the subjects were white, no further analyses examining the distribution of *APOE* genotype among ethnic groups were deemed necessary.

Numbers of patients without psychiatric symptomatology at first evaluation who were used in each Cox model are shown in table 2. In addition, table 2 presents numbers and percentages of subjects who developed incident psychiatric symptomatology at follow-up visits overall and by *APOE* genotype.

Cox analyses

Survival analyses have the advantage of combining information about both frequency of events (as in table 2) and time of occurrence of events. Patients without any ε4 alleles constituted the reference group in all subsequent Cox analyses, the results of which are presented in table 3.

Simple model—The presence of one ε4 allele was associated with a relative risk (RR) of 2.5 (95% CI 1.3 to 4.8) for subsequent development of delusions. Cumulative hazard curves are presented in the figure. There was no significant association between *APOE* status and either hallucinations, illusions, depression, or behavioral symptoms.

Adjusted model—In these analyses, age, ethnicity, sex, education, disease duration, mMMSE score, and BDRS score were simultaneously introduced as covariates in Cox models. The presence of one ε4 allele was associated with an RR of 3.0 (95% CI 1.4 to 6.3) for development of delusions. When two ε4 alleles were present, there was an 11.7 RR (95% CI 3.8 to 36.0) for development of delusions. Analyses for the other psychiatric symptoms did not reveal any significant associations with the *APOE* genotype, except for a negative correlation between the presence of two ε4 alleles and the development of hallucinations (RR 0.2; 95% CI 0.0 to 0.9).

Discussion

Many studies failed to detect any association between *APOE* genotype and either delusions or psychosis in patients with AD.[12,16,17,19-24,26] On the contrary, other studies[11,15] have reported an increased frequency of psychosis in ε4 carriers. Similarly, it has been shown that ε4 was associated with psychosis (in particular, at the advanced stages of the disease),[14] and an increased frequency of hallucinations and psychotic disturbances has been noted in patients with AD with the ε4 allele.[13]

Our key finding was a strong and dose-related association between the *APOE* genotype and the incidence of delusions. We also noted that the presence of two ε4 alleles was associated with a decreased risk for developing hallucinations (RR 0.2; 95% CI 0 to 0.9; $p < 0.04$) in the adjusted model only. This was not seen with one ε4 allele in the same model (RR 0.9; 95% CI 0.4 to 1.9; $p < 0.71$). In addition, this effect was not seen for one or two ε4 alleles in the unadjusted model. Given this weak association, the implications of this finding are unclear. One possible explanation is that treatment during follow-up with either antipsychotic or anticholinesterase medications in subjects with one or two ε4 alleles (who might have received these treatments because of more delusions) might have resulted in suppression of hallucinations and therefore artificially decreased incidence. To test this idea, we excluded subjects who received any of the above medications and repeated the analyses. The protective effect was no longer present (simple model—one ε4: RR 1.7, 95% CI 0.72 to 4.02, two ε4: RR 0.5, 95% CI 0.11 to 2.28; adjusted model–one ε4: RR 1.3, 95% CI 0.45 to 3.53, two ε4: RR 0.5, 95% CI 0.9 to 2.72), supporting this possibility. The results for delusions remained unchanged. Alternatively, there might be a real dissociation between the incidence of delusions and hallucinations. This would not be surprising given that we observe this dissociation in AD (where delusions are more common than hallucinations) and in diffuse Lewy body dementia (where hallucinations are more common than delusions). It may suggest differential pathophysiology or pathoanatomic localization underlying the development of these symptoms.

With regard to other psychiatric manifestations in AD, some studies did not detect any association between *APOE* genotype and depressive symptoms in AD samples.[18,19,23,25,26] *APOE* genotype was not associated with any changes in depression scores in healthy elderly

community residents.[27] However, it has been reported that patients with AD with ε3/ε4 genotype were more likely to be depressed[11] and that a positive correlation exists between the ε4 allele and mood disturbances.[13] Unlike the previous studies, an increased risk for depression in carriers of the ε2 (rather than the ε4) allele[12] and a protective role for the ε4 allele for depressive symptoms[15] have been published. The current study failed to detect any association between *APOE* genotype and depressive symptomatology.

Behavioral disturbances have also been investigated in relation to *APOE* genotype. Although agitation was more common in ε4 carriers in one study,[10] in a subsequent study, agitation and disorientation were more common in ε4/ε4 carriers, whereas anxiety and sleep disorders were more common in ε3/ε4 carriers.[3] In another report, it was noted that the presence of the ε4 allele was associated with increased combativeness, agitation, wandering, and confusion.[13] We detected no association between the *APOE* genotype and incidence of behavioral disturbances in our cohort.

Explanations for the variable findings in previous studies include differences in patient populations (some of the studies included subjects with Lewy body disease), differences in the assessment of psychiatric symptomatology, and possible lack of statistical power to detect associations in the negative studies. In addition, many of the above studies did not control for potential confounding variables. Most important, all of the previous studies were cross-sectional, whereas the current study evaluated risk for incident symptoms in a prospectively followed cohort.

The current analyses are performed on a well-characterized sample of patients with probable AD who underwent a rigorous diagnostic process in AD research centers. Patients with a diagnosis of diffuse Lewy body disease or other dementias were not included. A widely used scale for psychopathology with well-documented reliability and validity was used. Additional strengths of the current cohort include enrollment of subjects who were at a relatively early stage of the disease and the long follow-up with semiannual recording of psychopathology. Thus, we have reliably recorded the progression of AD from its early stages, and we have accurately assessed the incidence of psychiatric symptoms.

We also tried to control for all potential confounders. Low educational attainment has been associated with high risk for developing AD[43] and psychosis in AD.[20] Similarly, female gender has been considered a risk factor in AD and has been related to *APOE* status.[20] We included both education and sex as covariates in our analyses. Because severity of AD might be associated with the risk for psychopathologic manifestations,[2,20] we controlled for cognitive (mMMSE) and functional (BDRS) impairment as well as age and disease duration.

Different *APOE* genotypes seem to confer different risks for developing AD (and therefore possible differential biologic effects) among different ethnic groups.[42,44] Given the fact that the ethnic distribution of this AD population was heavily weighted for white persons, with few blacks or Hispanics, the results of the current study might not be generalizable to all ethnic groups. In addition, the population was derived from major university-based AD referral centers, and it might not be generalizable to the population of patients with AD in the community. Finally, it is plausible that the modest sample size of 87 subjects might have resulted in inadequate power to detect associations between the *APOE* genotype and illusions, hallucinations, depression, and behavioral symptoms.

The clinical heterogeneity observed in AD[45] could derive from underlying genetic variability. For example, the presence of the ε4 allele has been associated with earlier age at disease onset.[41] The relation of *APOE* genotype to extrapyramidal signs in AD has also been investigated. Psychotic manifestations and extrapyramidal signs are well-characterized predictors of rate of progression and outcomes in AD.[7-9] The presence of the ε4 allele was

associated with increased risk for psychosis in the current study but has been inversely associated with the development of extrapyramidal signs in previous reports.[46] Finally, the association between the *APOE* genotype and rate of cognitive decline or outcomes in AD has been controversial.[7,41,46,47]

In terms of neuropathologic correlates, patients with AD with the ε4 allele have increased β-amyloid burden.[48,49] Psychiatric symptomatology has been associated with more severe neuropathologic changes.[50,51] It is therefore plausible that the increased incidence of delusions in subjects with ε4 alleles could be a manifestation of more severe underlying pathology.

The ε4 allele has been associated with more profound deficits in cholinergic neurons, in particular in the frontal lobes,[52,53] whereas the development of psychiatric symptoms in AD appears to be related to specific neurotransmitter imbalances, notably acetylcholine.[54] Consequently, the presence of the ε4 allele could favor a preferential pathologic involvement of the cholinergic system, which in turn might result in more frequent psychiatric manifestations.

Psychotic manifestations in AD have been associated with pathology in the temporal lobe and hippocampus.[50,55] SPECT evidence has suggested that delusions in AD may be associated with greater temporal lobe hypoperfusion.[56] At the same time, SPECT and MRI studies have shown greater atrophy in medial temporal structures and more severe loss in hippocampal volumes in patients with AD carrying the ε4 allele.[57,58] It is conceivable that the detected association between *APOE* genotype and delusions might reflect neuropathology more heavily concentrated in the temporal lobe. Despite these speculations, the pathophysiologic explanation of the association between the *APOE* genotype and development of delusions in AD is not clear.

The observed association between the *APOE* geno-type and development of delusions is important, given the medical and social impact of psychiatric symptomatology in AD, its prognostic value for future outcomes, and the responsiveness of psychosis in AD to treatment.[59-62]

Acknowledgments

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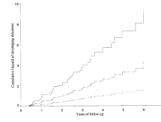
Figure.
Cumulative hazard curves for developing delusions according to APOE genotype. The time axis is years from first evaluation until development of delusions (or last evaluation). Solid line = subjects with two ε4 alleles; long dashed line = subjects with one ε4 allele; short dashed line = subjects with no ε4 allele.

Table 1

Demographic, APOE, clinical, and neuropsychologic information at first evaluation for all subjects, n = 87

Data	n
Men (%)	47 (54)
Women (%)	40 (46)
Ethnicity	
white (%)	78 (89.7)
black (%)	4 (4.6)
hispanic (%)	5 (5.7)
Mean age (SD), y	70.7 (7.8)
Mean duration of disease (SD), y	3.9 (2.1)
Mean education (SD), y	13.6 (3.7)
Mean mMMSE (SD)	37.8 (6.2)
Mean BDRS (SD)	7.7 (3.2)
Two ε4 alleles (%)	13 (14.9)
One ε4 allele (%)	35 (40.2)
No ε4 allele (%)	39 (44.8)

mMMSE = modified Mini-Mental State Examination; BDRS = Blessed Dementia Rating Scale.

Table 2

Numbers and percentages of patients manifesting incident psychiatric symptoms at any follow-up visit, overall and within each APOE *genotype group*

Incident psychiatric symptoms	No. of subjects overall		No. (%) of subjects manifesting symptom			
	No symptom at first visit	Manifesting symptom at follow-up	Two ε4 alleles	One ε4 allele	No ε4 allele	*p* Value
Delusions	58	49	8 (100)	21 (95.5)	20 (71.4)	0.028
Hallucinations	77	35	2 (16.7)	18 (56.3)	15 (45.5)	0.063
Illusions	81	17	4 (30.8)	5 (15.6)	8 (22.2)	0.512
Depression	49	36	3 (42.9)	15 (78.9)	18 (78.3)	0.140
Behavioral	38	36	6 (100)	10 (100)	20 (90.9)	0.464

p Values are derived from χ² analyses of the following two variables: development of psychiatric symptomatology and *APOE* genotype group.

Table 3

Cox proportional hazards models predicting psychiatric symptomatology by APOE *genotype*

Type of analysis	Psychiatric symptom	RR (95% CI) when presence of one ε4 allele	RR (95% CI) when presence of two ε4 alleles
Simple model	Delusions	2.5 (1.3–4.8)[*]	5.6 (2.2–14.0)[*]
	Hallucinations	1.2 (0.6–2.5)	0.3 (0.1–1.3)
	Illusions	0.6 (0.2–1.7)	1.4 (0.4–4.7)
	Depression	1.0 (0.5–2.0)	0.3 (0.1–1.1)
	Behavioral	1.3 (0.6–2.8)	0.8 (0.3–2.1)
Adjusted model	Delusions	3.0 (1.4–6.3)[*]	11.7 (3.8–36.0)[*]
	Hallucinations	0.9 (0.4–1.9)	0.2 (0.0–0.9)[*]
	Illusions	0.5 (0.1–1.7)	1.2 (0.3–5.2)
	Depression	2.4 (1.0–5.8)	0.4 (0.1–1.6)
	Behavioral	1.4 (0.5–3.8)	1.5 (0.6–4.3)

Results for both the simple model (*APOE* genotype being the predictor without inclusion of other covariates) and the adjusted model (age, sex, ethnicity, disease duration, modified Mini-Mental State Examination, and Blessed Dementia Rating Scale score included as covariates) are presented.

RR = relative risk.

[*] Significant results.