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A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease

Article abstract—We evaluated the frequency of depression and psychosis in 46 patients with AD and 135 control subjects with the apolipoprotein (APO) E3/3 or E3/4 genotype. Patients with AD and the *APOE3/4* genotype had a more than threefold increase in the signs of depression and psychosis when compared with either patients with the *APOE3/3* genotype or to control subjects. Our preliminary study suggests that the phenotype of AD associated with the ε4 allele is more likely to include psychiatric manifestations.

NEUROLOGY 1996;47:256–259

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The ε4 isoform of the apolipoprotein (apo) E gene is associated with AD.[1] Evaluation of the clinical phenotypes of AD with isoforms of the *APOE* gene may offer insight into possible roles of the apoE4 protein in AD. Lopez-Alberola et al.[2] found no differences in the psychiatric, demographic, neurologic, or neuroimaging features of 31 AD patients with the *APOE4/−* genotype and 31 AD patients with other *APOE* genotypes. However, the study was small, control subjects were not included, and the frequency of other alleles was unspecified.

We hypothesized that patients with AD and the ε4 allele would be phenotypically different from patients with AD without the ε4 allele and from control subjects. We focused on the presence or absence of psychiatric manifestations because the frequency of depression and psychosis is high in patients with AD[3-5] and disturbances in neuronal circuitry and neurotransmitter imbalances are common to both AD and psychiatric illnesses and therefore proteins such as apoE may influence psychiatric manifestations in AD.

Methods. Data were available from a previously described, community based, longitudinal study of the elderly, representative of individuals over 65 residing in the area.[6] All subjects had a neuropsychological battery, a 17-item Hamilton Depression Rating Scale (HDRS), and a screen for psychosis adapted from the Screening Clinical Interview with the DSM-III-R (SCID). A diagnosis of probable AD was made using the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease Related Disorders Association criteria. The severity of cognitive impairment was assessed by the clinical dementia rating scale (CDR), the total recall score on the Bushke selective reminding memory test, and the Blessed cognitive score.[6,7]

Patients were excluded from the study if they had genotypes other than *APOE3/3* or *APOE3/4,* because these genotypes were less frequent or if they had possible AD (implying a potential additional cause for their dementia). We included patients with AD and a CDR between 0.5 (very mild AD)[8] and 2 (moderate AD). Subjects were divided into four categories based on the *APOE3/3* or *APOE3/4* genotype and the presence or absence of AD.

For depression, we evaluated the total HDRS score. For psychosis, we used questions dealing with delusions and hallucinations from the adapted SCID pooled for an overall psychosis score with 1 point for each affirmative answer (maximum score of 3). Scores were evaluated both as continuous and categorical variables. For the categorical variables, we used a cutoff score of 10 or more for the HDRS (60% sensitivity and 88% specificity for the diagnosis of major depression in patients with AD)[9] and psychosis was rated as present or absent.

Demographic variables were analyzed using the Student's *t*-test or χ^2 analysis and Fisher's exact tests. With control subjects of the *APOE3/3* genotype as reference, the scores as continuous outcome variables were analyzed using analysis of variance, with and without adjusting for age, education and severity of dementia (using CDR, total recall, or Blessed score). The presence or absence of the dichotomized categorical outcome variables of HDRS and psychosis scores were analyzed using χ^2 analysis, Fisher's

Table 1 *Demographic characteristics*

Variable	Subjects by diagnosis			Subjects by genotype		
	Control subjects (CI)	Patients (AD)	*p*	*APOE3/3*	*APOE3/4*	*p*
Number of subjects	135	46	—	124	57	—
Age ± SD	73.9 ± 6.8	79.2 ± 7.3	0.0000	74.7 ± 7.1	76.6 ± 7.6	0.11
(range) (yrs)	(58–93)	(65–96)		(58–93)	(65–96)	
Gender						
Male	32 (23.7%)	10 (21.7%)	0.79	33 (26.6%)	9 (15.8%)	0.11
Female	103 (76.3%)	36 (78.3%)		91 (73.4%)	48 (84.2%)	
Education ± SD	8.4 ± 4.6	5.3 ± 4.0	0.0001	7.9 ± 4.6	6.9 ± 4.7	0.19
(range) (yrs)	(0–20)	(0–12)		(0–20)	(0–18)	
Ethnicity						
Afr. Amer.	36 (26.7%)	13 (28.3%)	0.12	26 (21%)	23 (40.4%)	0.02
Caucasian	26 (19.3%)	3 (6.5%)		23 (18.5%)	6 (10.5%)	
Hispanic	73 (54.1%)	30 (65.2%)		75 (60.5%)	28 (49.1%)	
CDR						
0	135 (100%)	0 (0%)	0.0000	98 (79.0%)	37 (64.9%)	0.13
0.5	0	20 (43.5%)		12 (9.7%)	8 (14.0%)	
1	0	18 (39.1%)		11 (8.9%)	7 (12.3%)	
2	0	8 (17.4%)		3 (2.4%)	5 (8.8%)	
Mean total recall	39.4 ± 7.6	22.3 ± 9.0	0.0000	35.9 ± 10.4	32.9 ± 11.8	0.10
score ± SD (range)	(23–59)	(0–41)		(0–59)	(2–56)	
Mean Blessed	4.2 ± 3.8	13.9 ± 6.5	0.0000	6.1 ± 5.8	8.0 ± 7.2	0.07
cognitive score ± SD	(0–17)	(2–28)		(0–24)	(0–28)	
(range)						

Afr. Amer. = African Americans; CI = cognitively intact control subjects; AD = Alzheimer's disease patients.

exact tests, and logistic regression analysis both before and after adjusting for age, education, and severity of dementia. The analysis was repeated among patients using *APOE3/3* patients as reference.

Results. Of 181 eligible subjects, 46 had AD (*APOE3/3* [26]; *APOE3/4* [20]) and 135 were control subjects (*APOE3/3* [98]; *APOE3/4* [37]) (table 1). We evaluated ethnicity because the association between *APOE4* and AD may differ among races.[1] There was no difference in the outcome variables of psychosis and HDRS scores among the different ethnic groups. Patients with AD and the *APOE3/4* genotype show higher HDRS and psychosis scores when compared with *APOE3/3* control subjects when scores were analyzed both as continuous (table 2) and as categorical (table 3) variables. The difference remained significant after adjusting for age, education, and severity of dementia and was not seen when *APOE3/4* control subjects or *APOE3/3* patients were compared with *APOE3/3* control subjects. When compared with patients with the *APOE3/3* genotype, patients with the *APOE3/4* genotype show higher HDRS and psychosis scores when the scores were analyzed as continuous variables, and these results approached significance when the scores were analyzed as categorical variables (see tables 2 and 3).

Discussion. Our results suggest that patients with AD and the *APOE3/4* genotype may have more psychiatric impairment than their peers with the *APOE3/3* genotype or control subjects of either genotype. The at least threefold increase in psychiatric symptomatology does not appear to be due to differences in age, education, or severity of dementia as it persisted after adjusting for them.

APOE4 increases risk of AD either by altering the properties of β-amyloid or tangle formation,[1] and this may predispose patients with the ϵ4 allele to increased frequency of psychiatric symptoms. Patients with AD and psychosis have an overall trend toward increased numbers of senile plaques (SPs) and tangles throughout the brain with more SPs in the presubiculum and increased neurofibrillary tangles in the middle frontal cortex as compared with AD patients without psychosis.[3] Patients with AD and depression show accelerated degeneration of the locus ceruleus and substantia nigra.[4] Autopsies on patients with AD and the ϵ4 allele[10] reveal overall increased numbers of plaques and tangles when compared with patients with AD and the *APOE3/3* genotype, with significant increases in SPs in the middle frontal, superior temporal, and inferior parietal areas and the CA1 area of the hippocampus that is near the presubiculum, although the substantia nigra and locus ceruleus were not examined.[10] The

Table 2 *HDRS and psychosis scores as continuous variables for all subjects using* APOE3/3-*CI subjects as reference and for patients only using* APOE3/3-*AD patients as reference*

Symptom	Group	Mean Score ± standard deviation (sd)	*p*	*p* value adjusted for age, education and CDR	*p* value adjusted for age, education and total recall score	*p* value adjusted for age, education and Blessed score
HDRS score	*APOE3/3*-CI	4.83 ± 4.78	Reference	Reference	Reference	Reference
	APOE3/3-AD	5.46 ± 4.12	0.20	0.17	0.73	0.75
	APOE3/4-CI	5.62 ± 3.90	0.43	0.44	0.41	0.42
	***APOE3/4*-AD**	**8.70 ± 6.30**	**0.002**	**0.002**	**0.01**	**0.02**
Psychosis score	*APOE3/3*-CI	0.36 ± 0.66	Reference	Reference	Reference	Reference
	APOE3/3-AD	0.35 ± 0.56	0.58	0.57	0.80	0.94
	APOE3/4-CI	0.57 ± 0.90	0.14	0.10	0.05	0.05
	***APOE3/4*-AD**	**0.90 ± 0.85**	**0.003**	**0.01**	**0.007**	**0.02**
HDRS score	*APOE3/3*-AD	5.46 ± 4.12	Reference	Reference	Reference	Reference
	***APOE3/4*-AD**	**8.70 ± 6.30**	**0.04**	**0.03**	**0.04**	**0.05**
Psychosis score	*APOE3/3*-AD	0.35 ± 0.56	Reference	Reference	Reference	Reference
	***APOE3/4*-AD**	**0.90 ± 0.85**	**0.01**	**0.01**	**0.02**	**0.01**

similarities in the neuropathologic profiles of patients with AD and the ϵ4 allele and patients with AD and psychopathology may help explain the increased frequency of psychiatric symptoms among patients with AD and the ϵ4 allele.

Neurochemically, patients with AD and psychosis have more noradrenaline in the substantia nigra and less serotonin in the subicular region of the brain.[3] Patients with AD and depression have reduced noradrenaline in the neocortex and trends toward reduced levels in all brain areas for both serotonin and noradrenaline.[5] The neurochemical pattern of patients with AD and the *APOE* isoforms has not been studied.

Patients with the ϵ4 allele have an earlier onset of AD.[1] We did not examine disease duration. Thus, the increased frequency of psychiatric symptoms may be explained by a longer duration of AD among our *APOE3/4* patients. However, this explanation is unlikely as symptoms such as depression and psychosis are poorly correlated with AD duration.[3-5] Also, by adjusting for age and severity of dementia, we effectively adjusted for differences in ages of onset of AD among genotypes. Hence, our results cannot be explained simply by differences in ages of onset or of duration of AD between groups. Alternatively, if we postulate the psychiatric symptoms to be influenced by SP deposition, SP deposition in AD is not correlated with illness duration.[1]

Table 3 *HDRS and psychosis scores as categorical variables for all subjects using* APOE3/3-*CI subjects as reference and for patients only using* APOE3/3-*AD patients as reference*

		Symptom					
Symptom	Group	Yes	No	OR	OR adjusted for age, education and CDR	OR adjusted for age, education and total recall score	OR adjusted for age, education and Blessed score
HDRS	APOE3/3-CI	16	82	Reference	Reference	Reference	Reference
≥/ 10	APOE3/3-AD	4	22	0.9 (0.3–3.1)	1.9 (0.4–10.1)	1.3 (0.3–5.4)	1.0 (0.2–4.2)
	APOE3/4-CI	5	32	0.8 (0.3–2.4)	0.8 (0.3–2.4)	0.9 (0.3–2.6)	0.9 (0.3–2.6)
	APOE3/4-AD	**8**	**12**	**3.4 (1.2–9.7)**	**8.1 (1.4–49.4)**	**4.4 (1.1–17.3)**	**3.5 (0.9–13.9)**
Psychosis	APOE3/3-CI	26	72	Reference	Reference	Reference	Reference
score ≥/ 1	APOE3/3-AD	8	18	1.2 (0.5–3.2)	1.7 (0.4–6.8)	1.5 (0.4–4.9)	1.6 (0.5–5.1)
	APOE3/4-CI	13	24	1.5 (0.7–3.4)	1.6 (0.7–3.7)	1.4 (0.9–4.5)	1.9 (0.8–4.4)
	APOE3/4-AD	**12**	**8**	**4.2 (1.5–11.3)**	**5.9 (1.2–30.0)**	**4.9 (1.4–17.3)**	**5.0 (1.4–18.0)**
HDRS	APOE3/3-AD	4	22	Reference	Reference	Reference	Reference
≥/ 10	**APOE3/4-AD**	**8**	**12**	**3.7 (1.0–14.8)**	**4.3 (1.0–18.9)**	**3.9 (0.9–17.3)**	**4.2 (0.9–18.9)**
Psychosis	APOE3/3-AD	8	18	Reference	Reference	Reference	Reference
score ≥ 1	**APOE3/4-AD**	**12**	**8**	**3.4 (1.0–11.4)**	**3.5 (1.0–12.2)**	**3.2 (0.9–11.0)**	**3.4 (1.0–11.9)**

Further evaluation of the clinical, neuropathologic, and neurochemical differences in AD with different isoforms of *APOE* may provide valuable information as to the role of the $\epsilon 4$ allele in the pathogenesis of AD.

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Supported by Federal Grants AG07232, AG10963, AG08702, and RR00645 and from the Charles S. Robertson Memorial Gift for Alzheimer's Disease Research from the Banbury Fund.

Received March 23, 1995. Accepted in final form January 2, 1996.

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