

Apolipoprotein E e4 allele is associated with extrapyramidal symptoms in Alzheimer's disease

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Background: Extrapyramidal symptoms (EPS) are not uncommon in Alzheimer's disease (AD). As apolipoprotein E(APOE) e4 allele is a major risk factor for late-onset AD, we intend to examine the association between APOE genotype and the development of EPS in AD.

Method: This study describes two hundred and fifty-five clinically diagnosed AD patients aged 72 to 80 years from 2010 to 2014. We reviewed the medical charts to determine the development of EPS. APOE genotypes were also confirmed.

Results: APOE e4 allele was detected in 74 patients (29%) and rigidity was among the most common EPS (61%). After adjusting the age, gender, baseline clinical dementia rating, we found AD patients carrying APOE e4 allele are more likely to develop EPS (OR: 4.515, $p=0.033$).

Conclusion: This study demonstrates the higher coexistence of EPS in AD patients with APOE e4 allele. Furthermore, the identification of APOE e4 allele in the development of EPS in AD patients supports the hypothesis that EPS may be partially attributed to AD pathology.

Keywords: Alzheimer's disease, extrapyramidal symptoms, apolipoprotein e e4

Introduction

Alzheimer's disease (AD) patients may develop EPS, alternatively termed parkinsonian-like symptoms or motor symptoms. This heterogeneous array of symptoms affects an estimated one-third of patients with clinically diagnosed AD; the symptoms include hypokinesia, rigidity, tremor, and gait disturbance.^{1,2,3} As mild cognitive impairment may be associated with an increased risk of AD, poorer lower-limb performance or gait disturbance may also increase the risk of AD in patients with mild cognitive impairment.⁴ In addition, EPS are associated with more a rapid development of AD, a heightened risk of poor prognosis, and earlier institutionalization.⁵ Pathological evidence has disclosed that the presence of EPS was postulated to represent neurofibrillary tangles (NFTs) or Lewy body accumulation across the neural systems.^{6,7} The presence of the *APOE* e4 allele may be also associated with the onset of AD. AD may be linked to amyloid trafficking and plaque clearance.^{8,9,10} however, the few studies that have investigated AD with *APOE* e4 allele have converged to reveal an estimated duration from disease diagnosis to the occurrence of EPS. In this study, we explore the influence of *APOE* e4 allele on the occurrence of EPS in a hospital-based cohort of AD patients.

Materials and methods

The data used in our analysis came from a study of 255 patients aged 70–90 years old, recruited from the outpatient clinic at Kaohsiung Ta-Tung Municipal Hospital.

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This investigation into the relationship between genes and AD was carried out from 2010 to 2014 and was approved by the Kaohsiung Ta-Tung Municipal Hospital Institutional Review Board (IRB-KMTTH-E(I)-20160142). All patients provided written informed consent, and that this study was conducted in accordance with the Declaration of Helsinki. Information on current medical conditions and any medications being taken by the patients was obtained. Two specialists (Yang YH, Chou MC) performed complete neurological examinations and cognitive function assessments on all patients. The motor symptoms of bradykinesia, rigidity, tremor, and gait disturbance were determined from a complete chart review (Chang YP). We also ascertained and excluded patient histories of neuroleptic, antidepressant, or other medications known to cause EPS. Patients were given a battery of neuropsychological tests, and individuals showing evidence of clinically significant cognitive impairment were determined as having AD by both our specialists (Yang YH, Chou MC) and neuropsychologist (Hsu CL).

APOE genotyping

Peripheral blood leukocytes were extracted for genomic DNA testing using a QIAamp blood kit (QIAGEN). A polymerase chain reaction (PCR) amplified exon 4 of the *APOE* gene with an upstream primer, 50' - TCG CGGGCCCCCGGGCCTGGTACA-30, and a downstream primer, 50' - ACAGAATTCGCCCCGGCCTGGTACAC TGCCA-30. The PCR products were digested with HhaI, and the fragments were separated by electrophoresis on a 6% polyacrylamide gel and ethidium bromide staining. The DNA fragments were visualized by UV illumination. The determination of *APOE* genotypes was carried out in a blinded fashion by scoring for a special combination of fragment sizes. Allele frequencies were estimated by counting the alleles and calculating sample proportions.

Statistics

A survival analysis model was constructed using the occurrence of EPS in all AD patients as an endpoint. In the analysis, we controlled age, gender, clinical dementia rating (CDR), and at least one copy of *APOE* allele. Beyond the descriptive analysis, we also performed a comparative analysis using the Cox regression model to assess the effects of these criteria on the occurrence of EPS in AD patients.

Table 1 Demographic data of alzheimer's disease patients

Alzheimer's disease patients (n=255)		
	Mean	SD
Age, years	80	8.0
Female, n	130	65.3
CDR, n (%)		
0.5	70 (27.5)	
1	128 (50.0)	
2	52 (20.0)	
3	5 (2.5)	
APOE e4, n (%)	74 (29)	
Education, years	7	4.8
MMSE	16.6	6.1

Abbreviation: CDR, clinical dementia rating assignment.

Results

For the present study, we selected 255 patients with a mean MMSE of 16.6, and a mean number of seven years spent in education. Among these patients, 29% (n=74) were found to carry at least one E4 allele. (Table 1) Based on the definition of the EPS of AD from previous published articles,² the percentages of hypokinesia, rigidity, gait disturbance, and tremor were 53%, 61%, 46%, and 15%, respectively. The percentage of patients found to have at least 1 e4 allele was 46%, which was higher in AD patients with EPS than the 29% found in AD patients without EPS. The Kaplan-Meier survival curve suggests that EPS occur three years after AD is clinically diagnosed. (Figure 1) Using the Cox regression model to control age, gender, and baseline CDR at the time of AD diagnosis, a significant increase of risk (odds ratio: 4.541, $p=0.033$) was discovered in the *APOE* genotype carrying e4 allele (Table 2).

Discussion

The current study examines the rate and frequency of *APOE* e4 allele carrier status in subjects with probable AD, who were separated into two groups: AD with EPS and AD without EPS. The distribution of EPS in our study is similar to that of previous reports.²

Several findings are of particular interest. First, the prevalence of EPS symptoms in our study (5%) were much lower than in previous reports (6–50%),¹¹ and thus, our results should be interpreted with caution; however, three specialists and one psychologist verified all of our AD patients as being properly diagnosed according to the common AD criteria,¹² and this

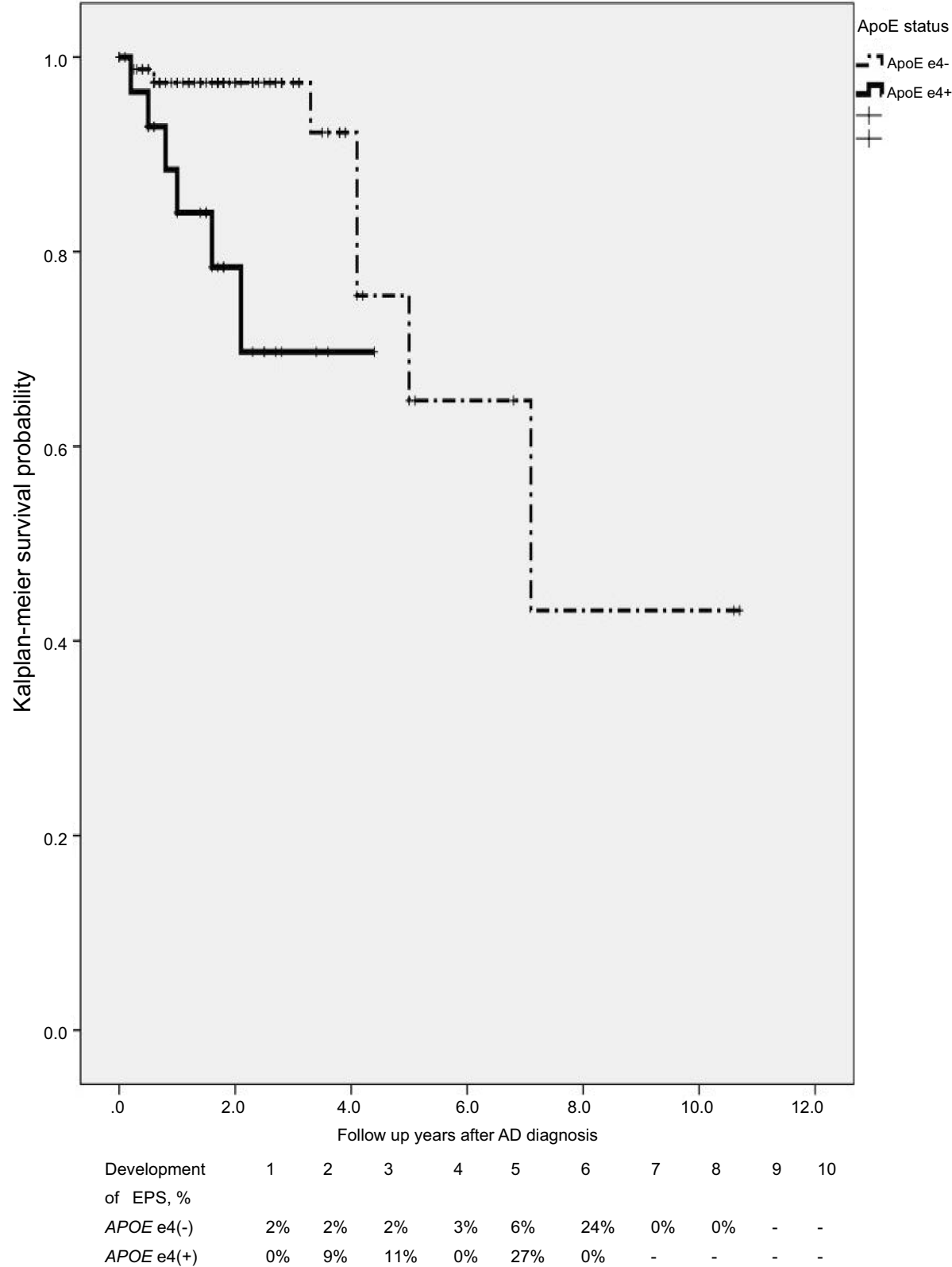


Figure 1 Kaplan-Meier survival curve of AD developing EPS. Log rank test ($\tau=8.14$, $p=0.004$).
Abbreviations: APOE, Apolipoprotein E; AD, Alzheimer's disease.

Table 2 Adjusted factors contributing to the development of EPS in alzheimer's disease patients

	OR	95% CI	p
Age	1.05	0.96–1.14	0.303
Gender	0.75	0.21–2.69	0.655
APOE e4	4.515	1.12–18.15	0.034
Initial dementia stage (CDR)			
0.5	1		
1	1.11	0.25–4.96	0.891
≥2	1.73	0.34–8.72	0.506

Abbreviation: CDR, clinical dementia rating.

allowed us to be confident with the accuracy of our diagnosis of AD, and EPS may be underestimated because of the relatively strict evaluations. Second, the AD patients carrying the *APOE* e4 allele may be more prone to developing EPS. The *APOE* e4 allele is associated with the development of NFTs in AD.¹³ Although the pathogenic role of NFTs in the development of EPS remains to be elucidated, neuropathological evidence suggests that AD patients with EPS may be subject to a different distribution of NFTs;⁶ and that the neuronal loss in substantia nigra, partly related to tau lesions, is a major pathological substrate of parkinsonian symptoms in AD patients.^{14,15} In contrast, pathological evidence shows the *APOE* e4 allele to be over-represented in Lewy body variants of AD patients; furthermore, coexisting Lewy body pathology has been found among AD patients.^{16,17} While previous studies show that *APOE* e4 alleles in AD were less likely to develop EPS,² Iqbal et al reported that the presence of EPS may not only be useful in discriminating between AD and non-AD controls, but also exhibits a distinct distribution in a subgroup defined by late-onset AD with the presence of one or two *APOE* e4 alleles.¹⁸ Because the *APOE* e4 allele is also associated with higher frequencies of neuritic and diffuse amyloid plaques in AD patients, it is therefore reported in line with severity in AD pathological findings.²⁰

Our study requires several caveats. First, our case numbers are relatively small compared to those of previous studies, and our study are based on clinical diagnosis of probable AD, without neuropathological examination. Second, although excluding the possibility of drug-induced events by analyzing detailed histories of previous neuroleptic or antiparkinsonian medications for all the patients in the present study, it should not be ruled out that EPS might be related to medication. Third, the possibility of Lewy body dementia cannot be excluded because of the lack of neuropathology data;¹⁹ however,

our strict diagnosis of AD patients and Lewy body dementia was excluded if EPS like parkinsonian symptoms occurred within one year of initial dementia diagnosis, in which case this issue would be rendered obsolete. The presence of small-vessel cerebrovascular disease cannot be excluded because not every AD patient takes brain magnetic resonance imaging;²¹ however, history of previous cerebrovascular disease and brain-computed tomography in AD patients was reviewed at the diagnosis stage.

In conclusion, *APOE* e4 allele may be associated increased risk of EPS in AD patients. Further large-scale longitudinal study may be performed to confirm the linkage.

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Disclosure

The authors report no conflicts of interest in this work.

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