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Effects of the Apolipoprotein E Genotype on the Therapeutic Response in Alzheimer's Disease Patients in Taiwan

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Abstract

Background: This retrospective research was conducted to analyze the impact of the apolipoprotein (Apo) Eε4 gene on the clinical response to donepezil among Taiwanese patients with Alzheimer's disease (AD).

Methods: Patients diagnosed with AD and treated with 5 mg of donepezil per day at the Neurologic Department of Kaohsiung Medical University Hospital from July 2003 to December 2013 were recruited as our study participants. Before treatment, the patients received neuropsychological tests, including the Mini-Mental State Examination (MMSE), the Cognitive Abilities Screening Instrument (CASI), the global Clinical Dementia Rating (CDR) scale, and the Clinical Dementia Rating Scale Sum of Boxes Score (CDR-SOB). Follow-up evaluation was performed every half year.

Results: In total, 76 AD patients with a mean age of 75.4 years ± 8.4 years were eventually recruited for this study. Twenty patients (26.3%) were ApoEε4 positive. Kaplan–Meier survival estimates of the time to functional decline for the ApoEε4-negative and the ApoEε4-positive groups were compared. Log-rank test results indicated that the ApoEε4-positive group had poorer treatment response with significant difference when function was measured using the CASI and global CDR ($p = 0.017$ and $p < 0.010$ respectively). After adjustment for age, sex, and educational attainment, the ApoEε4 status still affected the time to functional decline.

Conclusion: In the Taiwanese population, ApoEε4 may be negatively associated with the treatment response in AD patients treated with donepezil. These findings suggest that a genotype test for ApoE in AD patients may facilitate therapeutic decision making by physicians and care-givers.

Keywords: Apolipoprotein E; Alzheimer's Disease; Mini-Mental State Examination; Cognitive Abilities Screening Instrument; Global Clinical Dementia Rating; Clinical Dementia Rating Scale Sum of Boxes Score

Introduction

In 2010, the number of people estimated to have dementia was approximately 35.6 million, and this number will nearly double every 20 years [1]. Alzheimer's disease(AD) is the most common type of dementia [1]. Although there is no cure for AD currently, there are drugs that can delay functional decline. Three types of acetylcholinesterase inhibitor (AchE-I), donepezil, galantamine, and rivastigmine and an N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, have been approved for use in AD patients by the US Food and Drug Administration (FDA)[2]. Donepezil has not only been approved to treat mild to moderate Alzheimer disease, and severe dementia [3].

In general, only 20% -70 % of AD patients benefit from drug treatment [4]. Various therapeutic responses have been reported among different races [5], including Taiwanese [4, 6]. Empirical studies have attempted to identify factors that can be used to predict treatment response to AchE-I, such as sex, educational attainment and age. Scacchi's study indicated that female AD patients responded more markedly than did males [7]. In the study by Wattmo, older individuals had a more effective treatment response to AchE-I; however, educational attainment had no effect on treatment response [8]. In another study [9], younger AD patients (age < 65 years) showed significantly greater improvement after 3 month of AchE-I treatment. Csernansky indicated that a smaller hippocampal volume and inward variation of the lateral and inferomedial portions of the hippocampal surface may be related to poorer treatment responses [10].

The apolipoprotein (Apo) Eε4 gene has been identified to increase the risk of developing AD, particularly at a younger age [11]. However, how this genotype influences the treatment response of acetyl-cholinesterase inhibitors in AD patients remains controversial [12,13]. Research conducted in Italy [12] suggested that AD patients carrying at least one epsilon4 allele can be predicted to be responders to donepezil therapy. Patterson [14] observed a more effective treatment response in ApoEε4-positive patients who had mild AD. However, the results only revealed a significant difference only at the

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Table 1: Demographic Characteristics of the Study Participants.

Participants	All participants (n = 76)	APOEε4(-)[e] (n = 56, 73.7%[f])	APOEε4(+)[e] (n = 20, 26.3%[f])	*p* value
Age, mean± SD , year	75.4± 8.4	75.6± 8.3	74.7± 9.9	0.693
Female, n	58(76.3%)	43(76.8%)	15(75%)	1.000
Educational attainment, mean± SD, year	6.6± 4.6	6.4± 4.6	6.9± 4.9	0.699
Cognitive test score				
CASI[a], mean± SD	54.6± 21.2	54.8± 20.9	53.9± 22.6	0.870
MMSE[b], mean± SD	15.7± 6.2	16.2± 6.2	14.3± 6.1	0.231
CDR[c] CDR:1 n (%) CDR:2 n (%)	 65 (85.5%) 11 (14.5%)	 47(84%) 9(16%)	 18(90%) 2(10%)	0.508
CDR-SOB[d], mean± SD	5.9± 2.8	5.8± 2.8	6.0± 2.8	0.796

[a]CASI: Cognitive Abilities Screening Instrument, range: 0~100
[b]MMSE: Mini-Mental State Examination, range: 0~30
[c]CDR: global Clinical Dementia Rating, range: 0~3
[d]CDR-SOB: Clinical Dementia Rating Scale Sum of Boxes Score, range: 0~18
[e]ApoEε4 +: Patients with 1 or 2 copies of the Apolipoprotein Eε4 allele
ApoEε4 - : Patients without the Apolipoprotein Eε4 allele
[f]%: out of all participantsa

second (3–9 months after treatment) and third visits (9–15 months after treatment); the difference became non significant at the fourth visit (15–24 months after treatment). However, in a study conducted in Japan, Kanaya indicated that ApoE4 might be a risk factor for worsening symptoms with respect to long-term prognosis [13]. To further clarify the effect the ApoE genotye exerts on the treatment response to AchE-I, we conducted this longitudinal study by using various measures to examine Taiwanese AD patients treated with donepezil.

Methods

Patients and evaluation

This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital in Taiwan. Patients diagnosed with AD and treated with 5mg of donepezil per day at the Neurological Department of Kaohsiung Medical University Hospital from July 2003 to December 2013 were recruited as the study participants. AD diagnosis was based on the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [15]. Before treatment, the recruited patients received a series of comprehensive neuropsychological examinations, including the Mini-Mental State Examination (MMSE) [16], the Cognitive Abilities Screening Instrument (CASI) [17], and the global Clinical Dementia Rating (CDR) scale [18] and the Clinical Dementia Rating Scale Sum of Boxes Score (CDR-SOB) [19]. These examinations were administered every 6 months to observe the treatment response to donepezil. A senior neuropsychologist and an experienced physician performed these tests by using information obtained from a knowledgeable collateral source (typically, a spouse or child). In addition, the demographic characteristics including age, sex, and educational attainment were also collected. ApoE genotyping was performed if the patient or their family agreed. Restriction enzyme isotyping was executed by following a modification of the protocol developed by Pyrosequencing (http://www.pyrosequencing.com). Patients with one or two copies of the ApoEε4 allele were grouped into the ApoEε4-positive group, and those without this allele were grouped into the ApoEε4-negative group.

Statistical analysis

SPSS for Windows, Version 14.0 (SPSS Inc., Chicago, IL,USA) was employed for statistical analysis. The level of statistical significance was set at 0.05 and all tests were two-tailed. The *t* test and chi-square test were performed to assess differences between the two groups (ApoEε4 positive, ApoEε4 negative). Kaplan–Meier survival estimates of time to clinically functional decline in these patients were compared. Higher global CDR and CDR-SOB scores and lower MMSE and CASI scores indicated poorer functioning. Therefore, we defined functional decline as a decrease in MMSE and CASI scores and an increase in global CDR and CDR-SOB scores compared with the baseline evaluation scores. The log-rank test was conducted to assess the differences among the scores. A Cox-regression model was

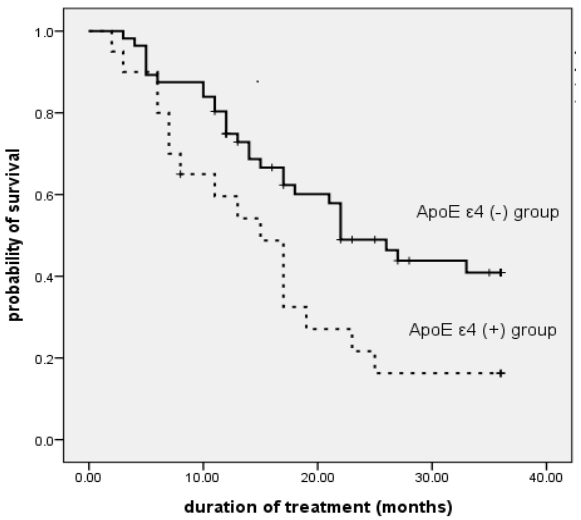

Figure 1: Kaplan–Meier survival estimates of time to clinically functional decline in CASI Score[a,b].
[a]functional decline: any decrease in CASI scores compared with baseline evaluation
[b]CASI: Cognitive Abilities Screening Instrument, range: 0~100
[c]p =0.017 by log-rank test

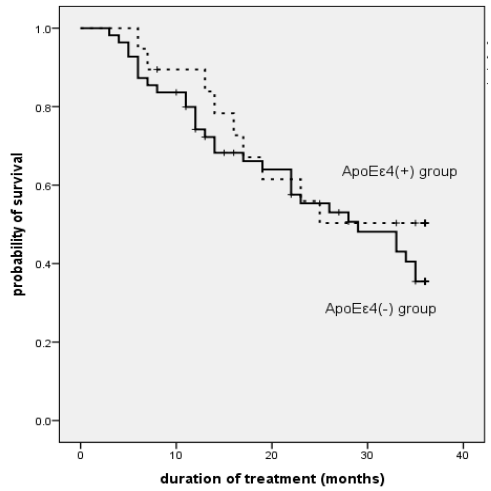

Figure 2: Kaplan–Meier survival estimates of time to clinically functional decline in MMSE Score[a,b].
[a]functional decline: any decrease in MMSE scores compared with baseline evaluation
[b]MMSE: Mini-Mental State Examination, range: 0~30
[c]p = 0.396 by log-rank test

used to adjust the effects of age, sex, educational attainment and ApoE genotype to the duration of treatment without functional decline.

Results

In total, 91 AD patients treated with donepezil were recruited for our analysis. However, 15 patients visit the hospital once only or did not complete the cognitive function tests required for analysis. A total of 76 AD patients with a mean age of 75.4 years were eventually recruited for the study. Among them, 20 patients (26.3%) were ApoEε4 positive. No significant differences in the demographic profiles were observed between the ApoEε4-positive and ApoEε4-negative groups. (Table 1) 96.1% of the participants has kept the drug treatment continuously throughout the first year; 69.7% of the participants continuously to the second year, and 48.7% of them have kept the drug treatment continuously till the end of third year.

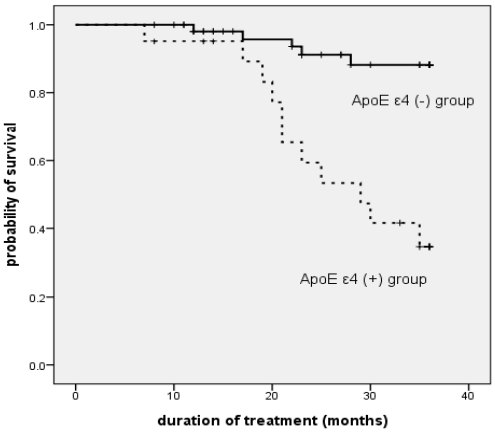

Figure 3: Kaplan–Meier survival estimates of time to clinically functional decline in CDR Score[a,b].
[a]functional decline: any increase in global CDR scores compared with baseline evaluation
[b]CDR: global Clinical Dementia Rating, range: 0~3
[c]p < 0.001 by log-rank test

Figures 1–4 depict the Kaplan–Meier survival estimates of time to functional decline among the ApoEε4-positive and ApoEε4-negative patients according to various cognitive function tests. When cognitive function was measured using the CASI, the median estimates of survival were 22.0 months (95% confidence interval [CI], 16.0–28.0) in the ApoEε4-negative group, and 15 months (95% CI, 10.0–20.0) in the ApoEε4-positive group. The log-rank test indicated that this difference was statistically significantly (p =0.017). The Cox regression and adjustment for age, sex, and educational attainment indicated that patients with ApoEε4 were 2.2 times more likely to exhibit functional decline than were those who were not Apoε4 carriers (95% CI for the hazard ratio [HR] = 1.16–4.19; p <0.05).

According to the MMSE model, the mean duration until functional decline was 25.9 months (95% CI, 21.3–27.8) and 24.7 months (95% CI, 20.9–31.0) in the ApoEε4-negative and ApoEε4-positive groups, respectively (Figure 2). The log-rank test (p = 0.396) and Cox regression model (p = 0.629) indicated no significant difference between the two groups.

In addition, we created Kaplan–Meier plots of the treatment response rate according to the global CDR score and CDR-SOB. According to the global CDR model, the mean duration until functional decline in the ApoEε4-negative group and ApoEε4-positive group was 32.4 months (95% CI, 32.6–35.7) and 27.4 months (95% CI, 23.5–31.3), respectively. The treatment response rate of the two groups differed significantly according to the global CDR model (p < .001) (Figure 3). After adjustment for age, sex, and educational attainment, ApoEε4 genotyping remained a significant predictor of survival (HR for clinically functional decline in the ApoEε4-positive group: 7.89; 95% CI: 2.59–24.08; p < .01).

According to the CDR-SOB model, the median duration until functional decline after treatment was 26 months (95% CI, 15.4–36.0) in the ApoEε4-negative group and 17.0 months (95% CI, 10.0–24.0) in the ApoEε4-positive group (Figure 3). No significant difference was observed between the two groups (p = 0.490). Further Cox

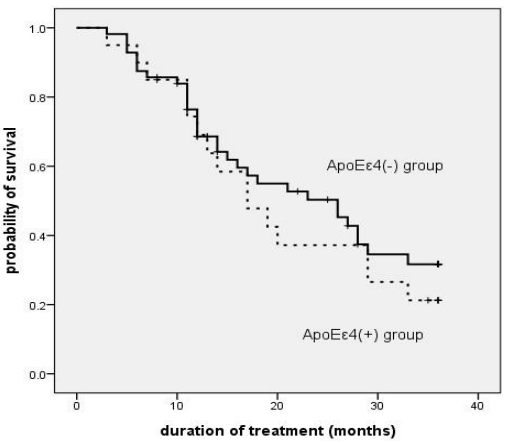

Figure 4: Kaplan–Meier survival estimates of time to clinically functional decline in CDR-SOB Score[a,b].
[a]functional decline: any increase in CDR-SOB scores compared with baseline evaluation
[b]CDR-SOB: Clinical Dementia Rating Scale Sum of Boxes Score, range: 0~18
[c]p = 0.490 by log-rank test

regression using age, sex, and educational attainment indicated that the odds ratio for developing functional decline between the ApoEε4-positive and the ApoEε4-negative groups was 1.42 with no significant difference (95% CI for the HR=0.76–2.65; p = 0.275). However, age subtly affected the survival rate. With ever 1-year increase, the odds of failure to respond to treatment increased 1.05 fold (95% CI: 1.01–1.09, p = 0.021).

Discussion

The results indicated that ApoEε4-positive AD patients treated with AchE-I had a more significant functional decline according to the CASI and global CDR scores than did ApoEε4-negative patients. In other words, ApoEε4-positive AD patients had poorer treatment response according to the difference in global CDR (p < .001) and CASI (p = 0.017) scores, but not according to MMSE (p = 0.396) and CDR-SOB (p = 0.490) scores. The differences in therapeutic response related to the ApoE gene status possibly resulted from differences in the measurements of therapeutic responses. Moreover, the differences in therapeutic response definitions might have caused variation in the therapeutic response results; this phenomenon has been discussed in previous studies [4,6].

A ceiling and floor effect has been observed when the MMSE is used to detect cognitive functional change [20]. It may fail to detect mild cognitive impairment, particularly among people with high educational attainment level (ceiling effect). In addition, it exhibits a limitation in detecting meaningful change in severe AD patients (floor effect). Therefore, the MMSE does not clearly reflect the change for treatment for these AD patients.

A previous study [14] reported that treatment response evaluated using the MMSE was related to the ApoE genotype. However, the response was not consistent throughout the treatment course, occurring only during some visits. Moreover, the response was limited in some stage of dementia, but not among all recruited patients. Such findings might be limited and cannot be applied entirely. The patients in our study had low initial MMSE scores; therefore functional change was not easily detectable using the MMSE.

The global CDR is a categorical variable, and progress in one category of the global CDR scale frequently represents obvious and dramatic functional change. This might explain the high survival rate in patients with functional decline in the ApoEε4- negative group when function was evaluated using the global CDR. By contrast, the survival curves exhibited different pattern when function measured using the CDR-SOB, which is the sum of the scores in each domain in the Global CDR, and ranges from 0.5 to 18. Because of the increased range of values, the CDR-SOB score can track the severity of changes among the stages of dementia [19]. However, subtle changes in the CDR-SOB score do not represent progression to a further global CDR category. Any subtle progression according to the CDR-SOB score is recorded as treatment failure. This may explain why the slope of the KM curve for the ApoEε4-negative group as measured using the CDR-SOB was steeper. Although the CDR-SOB has been examined less frequently in the literature, we analyzed and compare it with the global CDR score.

The APOEε4 gene has been identified as a risk factor for developing AD at a younger age [11], and its pathology and etiology have been considered to be related to amyloid deposits [21, 22]. Compared with ApoEε4-negativeAD patients, ApoEε4-positive patients had more amyloid deposits that developed earlier. In vitro, ApoEε4 less effectively inhibited amyloid beta protein aggregation than did ApoEε3. ApoE is crucial for neurite maintenance, but ApoEε4 mice had little neurite maintenance [21]. This pathology might explain some of our observation: ApoEε4- positive AD patients exhibited more rapid functional decline despite treatment.

The ApoE2 was considered a possible protective factor for Alzheimer's disease in some studies [23]; However, the results are not consistent, especially in Chinese [24]. Therefore we did not analyze the effects of APOE 2 in the therapeutic effects.

The study had several strengths. First, this is the first Taiwanese analysis between the relationship of ApoEε4 genotype and the treatment response in Taiwanese AD patients. Second, AD is a progressive disease; the follow-up duration in this study was a maximum of 3 years, enabling us to obtain the treatment responses that were similar to that in real clinical conditions. Third, we analyzed intra-individual differences, rather than the mean scores of the study participants. Finally, we evaluated the functional change in AD patients by using four scales frequently employed to investigate AD. Most previous researches have used only 2 measurements.

However, this study also has some limitations. First, the sample size was relatively small. Second, this was a retrospective study, the data for which were collected from hospital medical records; thus the actual compliance to treatment was difficult to confirmed from these records. A larger-scaled and prospective study should be conducted in the future.

Conclusion

The results indicated that ApoEε4 genotyping significantly affects the longitudinal treatment of AD patients treated with donepezil. However, the effects may differ according to the measurements used. These findings may provide the new information that can facilitate decision making by physicians and caregivers regarding the treatment of AD in Taiwanese patients.

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