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CLINICAL STUDY

Frequencies of apolipoprotein E alleles in depressed patients undergoing hemodialysis – a case-control study

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Abstract

Objective: To explore the relation between the frequencies of apolipoprotein E (ApoE) alleles and the occurrence of depression in patients undergoing hemodialysis in a Chinese population. *Methods*: We examined the ApoE alleles in a sample of 288 subjects: 72 patients with depression under hemodialysis, 74 patients without depression under hemodialysis, 75 patients with depression under nondialytic treatment and 67 patients without depression under nondialytic treatment. The depression state was assessed using the Center for Epidemiological Studies Depression (CES-D) scale. Associations between the occurrence of depression and the frequencies of ApoE alleles were examined using multinomial logistic regression models with adjustment of relevant covariates. Information about sociodemographics, clinical data, vascular risk factors and cognitive function was also collected and evaluated. *Results*: The frequencies of ApoE-ε2 were significantly different between depressed and non-depressed patients irrespective of dialysis ($p < 0.05$), but no significant difference was found in the frequencies of ApoE-ε4 ($p > 0.05$). Serum ApoE levels were significantly different between depressed and non-depressed patients in the whole sample ($p < 0.05$). Multinomial logistic regression models showed significant association between the frequency of ApoE-ε2 and the occurrence of depression in the Chinese population after control of relevant covariates, including age, sex, educational level, history of smoking and drinking, vascular risk factors and cognitive function. *Conclusions*: No association between the frequency of ApoE-ε4 and the occurrence of depression was found in patients undergoing hemodialysis. Further research is needed to find out if ApoE-ε2 acts as a protective factor in Chinese dialysis population since it might decrease the prevalence of depression and delay the onset age.

Keywords

Apolipoprotein E allele, depression, end-stage renal disease, hemodialysis, vascular depression

History

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Introduction

Depression is the most widely acknowledged psychological problem among the end-stage renal disease (ESRD) patients.[1,2] It is a major cause of death and significantly influences the quality of life among dialysis patients. As it is well-known, the two main types of depression are major depressive disorders (MDDs) and vascular depression (VD). Clinical and functional studies consider MDDs and VD as different neurobiological processes. MDDs attack about 28% of chronic kidney disease patients facing impending dialysis, and affect even a larger proportion of dialysis patients.[3] The term VD has been used to describe late-life depressive disorders in patients with clinical and neuroimaging evidence of cerebrovascular disease. About 54% of the patients with late-life depressive disorders meet the criteria for VD.[4]

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Hemodialysis patients are more prone to cardiovascular complications, accompanied by a higher incidence of depression or depressive symptoms. The presence of cardiovascular disease (CVD) is associated with worse cognitive performance in hemodialysis patients,[5] and cognitive impairment is closely corrected with depression.[6,7] Moreover, apolipoprotein E (ApoE) genotype can predict the cardiovascular end points in dialysis patients by affecting the cholesterol level.[8] Thus, depression or depressive symptoms may be tied to the effects of ApoE, but the frequencies of ApoE alleles vary across populations worldwide. ApoE has three major isoforms (ApoE2, ApoE3 and ApoE4) encoded by three alleles (ε2, ε3 and ε4, respectively). It is, therefore, imperative that the frequencies of ApoE alleles should be studied from different perspectives, including disease states, populations and geographic locations. Evidence suggests that ApoE2 may be the most beneficial ApoE isoform, while ApoE4 carries the highest risk of neurodegeneration.[9] However, little support for a direct association between ApoE and MDDs[10] or depressive symptoms[11] has been found. And it is still unclear whether the higher incidence of depression is tied to higher occurrence of

vascular complications, or that ApoE influences the occurrence of MDDs through vascular risk factors or cognitive function. Moreover, the association between the ApoE alleles and the occurrence of depression in dialysis populations has never been investigated.

Thus, in the present study, we examine a sample of dialysis patients and probe into the association between the frequencies of ApoE alleles and the occurrence of MDDs in patients after treatment with hemodialysis.

Methods

Participants and division

This case-control study involved a total of 288 patients (aged 18–65 years old) from our hospital. All dialysis patients who had received HD for more than 3 months and had MDDs during the current depressive episode were included. A written informed consent was obtained from all participants (or their caregivers) after full explanation of the study protocol, which had been approved by the Scientific Ethical Committee from our hospital (Approval No. 2013045).

There were four exclusion criteria: (1) Cognitive deficits such as considerable memory loss, confusion/dementia, Alzheimer's disease and intellectual disability; illiteracy and/or incapability of answering the questionnaire (difficulty in understanding the questions, visual or hearing impairment); (2) Depressive symptoms before dialysis; (3) Vascular depression (VD); (4) Above age 65, since advantaged age is a major risk factor for MDDs. Specifically, VD was defined according to the proposed diagnostic criteria as follows:[12,13] (1) depression occurs after the age of 65 or changes in the course of depression following a vascular disease in people with early-onset depression; (2) magnetic resonance imaging (MRI) findings show when presence of infarcts or lacunde; (3) there is evidence of a history of at least 3 of 8 vascular risk factors: hypertension, heart disease, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, smoking and obesity (These factors were defined according to two previous studies).[14,15]

The patients were divided into four groups: 72 patients with depression under hemodialysis (Group I), 74 patients without depression under hemodialysis (Group II), 75 patients with depression under nondialytic treatment (Group III) and 67 patients without depression under nondialytic treatment (Group IV).

Depression evaluation

Depression is a condition characterized by depressed mood or loss of interest or pleasure in nearly all activities almost every day for at least 2 weeks. MDDs were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. The presence of depressive symptoms was determined using the Center for Epidemiological Studies Depression (CES-D) scale.[16] All patients were diagnosed with MDDs by two experienced neurologist, psychiatrist or neuropsychologist separately. No patient was informed about his/her ApoE allele so as not to induce the impact of awareness on the mood.

Cognitive function assessment

The Chinese Version of the Mini-Mental State Exam (MMSE) was applied to assess the cognitive functions for each patient. The exam assessed a broad range of functions, including orientation, attention/calculation, registration, recall and language. The total score for MMSE is 30 points and a score less than 24 points indicates cognitive impairment.[17] To limit patients' fatigue, all exams were completed during the 1st hour after hemodialysis.

ApoE genotyping and measurement of serum ApoE

ApoE alleles in all the participants were measured by agarose isoelectric focusing immunoblots described by Chiang.[18] About 10 mL of peripheral blood was collected from each participant. Total RNA was extracted from mononuclear blood cells isolated using Takara's Trizol reagent and was then reversely transcribed into cDNA using a Takara's kit according to the manufacturer's instructions (ABI 7900 Taqman® system). Serum ApoE was evaluated using an enzyme-linked immuno-sorbent assay (ELISA) kit (Uscn Life Science Inc.) according to the manufacturer's recommendations. Standard curve contents were calculated in triplicate for each plate.

Demographic and clinical data at baseline

Demographic data including employment status, education status and history of drinking/smoking were collected by questioning the patients. Information concerning age, sex, health insurance and vascular risk factors was gathered from medical records. Blood was collected according to a standard protocol. Laboratory data concerning blood lipid and high sensitive C-reactive protein (hsCRP) (HITACHI 7180 Japan) were gathered from medical records.

Statistical analysis

All values were expressed as mean ± standard deviation (SD), or percentage, as appropriate, and $p < 0.05$ was considered significant ($\alpha = 0.05$ in two-tailed). Inter-group difference in continuous variables was evaluated by one-way analysis of variance (ANOVA) and Student–Newman–Keuls (SNK) multiple comparisons and differences in proportions were tested using Pearson chi-square test (χ^2) as appropriate. Frequencies of alleles were estimated by assessing the frequencies of phenotypes. The distributions were analyzed using Pearson's χ^2 test and Fisher's exact test as appropriate.

Association between distribution of ApoE alleles and depression was calculated by multinomial logistic regression models with adjustment for age, sex, educational level, history of drinking and smoking, vascular risk factors and cognitive function. The association was expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We also examined the subgroups divided by age span (aged 18–44 and 45–65). All statistical analyses were performed on SPSS 18.00 (IBM Corporation, Armonk, NY).

Results

Baseline characteristics

The 288 Chinese participants were aged 47.7 ± 12.2 years old on average. Their demographic and socioeconomic characteristics are shown in Table 1. No significant difference was observed concerning age, sex, educational level, employment status, history of drinking and smoking or other characteristics among the four groups. The onset ages of depression were slightly different between Group I and Group III. The vascular risk factors are significantly different among the four groups ($p < 0.05$), especially between dialysis and non-dialysis patients ($p < 0.05$).

Multinomial logistic regression analyses between ApoE allele and depression

The data about ApoE genotype, allele frequencies, serum ApoE level, CES-D score and cognitive function are shown in Table 2. Among the four groups, the frequencies of ApoE-ε4 are about 23.6%, 24.3%, 22.7% and 22.4%, respectively, which are not significantly different. The frequencies of ApoE-ε2 in Group I and Group III are significantly lower compared with Group II and Group IV ($p < 0.05$). The serum ApoE contents are significantly different between the depressed and non-depressed participants in the whole sample ($p < 0.05$). Moreover, the patients under hemodialysis irrespective of depression are prone to have cognitive impairment.

The relation between the frequency of ApoE and the occurrence of MDDs was further investigated using multinomial logistic regression analyses. The associations between the frequency of ApoE-ε2 and the incidence of depression were not significantly affected after controlling relevant covariates, including age, sex, educational level, history of drinking and smoking, vascular risk factors and cognitive function ($p > 0.05$) (Table 3). In comparison, the associations between the onset age of depression and the frequency of ApoE-ε2 were slightly weakened by controlling these covariates ($p < 0.05$). This dataset also showed no association between the frequency of ApoE-ε4 and the occurrence of depression in the Chinese dialysis population.

Discussion

This case-control study was conducted to investigate the relation between ApoE allele and depression in patients after treatment with hemodialysis. Our findings are consistent with some previous studies, including two large studies,[10,19] which did not show any relation between ApoE-ε4 frequencies and depression in European populations. Then they concluded that the relation between ApoE frequencies and depression risk was more modest. In our study, about 23.1% of the depressed patients and 23.4% of the non-depressed patients were

Table 1. Socio-demographic and clinical data of the participants.

Characteristics	Group I ($N = 72$)	Group II ($N = 74$)	Group III ($N = 75$)	Group IV ($N = 67$)	p-Value
Age (year)	49.2 ± 10.9	47.1 ± 13.4	46.3 ± 11.7	48.2 ± 12.8	0.33
Age at onset (year)	46.5 ± 8.9	–	48.7 ± 10.3	–	0.04
Sex (% Female)	62.5	63.5	61.3	59.7	0.92
Married (%)	84.7	85.1	84.0	85.1	1.00
Employed (%)	63.9	64.9	64.0	65.7	1.00
Health insurance (%)					0.98
Medical insurance	66.7	68.9	69.3	67.2	
New rural insurance	33.3	31.1	30.7	32.8	
Education (%)					1.00
Up to high school	20.8	21.6	21.3	20.9	
Beyond high school	79.2	78.4	88.7	89.1	
Living alone (%)	5.6	5.4	6.7	6.0	0.59
Family history of mood disorders (%)	15.3	10.8	14.7	11.9	0.83
Drinking (%)					0.13
Former	50.0	37.8	41.3	40.3	
Current	29.2	31.1	37.3	46.3	
Never	20.8	31.1	21.4	13.4	
Smoking (%)					0.95
Former	31.9	28.4	26.7	26.9	
Current	4.2	4.0	6.7	7.4	
Never	63.9	67.6	66.6	65.7	
Vascular risk factors	4.2 ± 1.8	3.9 ± 2.1	2.3 ± 0.9	2.1 ± 0.9	0.02
LDL-C (mmol/L)	3.4 ± 0.6	3.2 ± 1.8	2.9 ± 1.7	3.0 ± 0.8	0.08
VLDL-C (mmol/L)	0.54 ± 0.26	0.49 ± 0.11	0.46 ± 0.08	0.52 ± 0.18	0.13
HDL-C (mmol/L)	1.18 ± 0.44	1.31 ± 0.36	1.22 ± 0.18	1.17 ± 0.33	0.26
AlB (g/L)	35.7 ± 8.7	35.2 ± 5.9	34.7 ± 4.3	36.6 ± 7.4	0.07
Hs-CRP (mg/L)	9.7 ± 3.3	8.8 ± 2.6	8.7 ± 3.3	7.9 ± 2.1	0.14
Mean hemoglobin (g/L)	11.4 ± 5.6	11.9 ± 4.1	12.1 ± 5.3	12.3 ± 3.7	0.21

Notes: Continuous variables are presented as means ± S.D, categorical variables as numbers with percentage. Differences in proportions were tested using Pearson chi-square test; differences in means were tested using analysis of variance and Student–Newman–Keuls (SNK) multiple comparisons.
N, number; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; HDL-high-density lipoprotein cholesterol; AlB, albumin; Hs-CRP, high sensitive C-reactive protein; CES-D score, the Center for Epidemiological Studies Depression scale. Vascular risk factors: hypertension, heart disease, diabetes mellitus, hypercholesterolaemia and peripheal vascular disease, smoking, obesity. Group I, patients with depression under hemodialysis; Group II, patients without depression under hemodialysis; Group III, patients with depression under nondialytic treatment; Group IV, patients without depression under nondialytic treatment.

Table 2. Percentage of apolipoprotein-E phenotypes and alleles, combinations by serum ApoE, CES-D score and cognitive function among the four groups.

Patient group	Group I ($N=72$)	Group II ($N=74$)	Group III ($N=75$)	Group IV ($N=67$)	p-Value
Phenotypes					0.001
e2/e2 (%)	4.2	2.7	1.3	9.0	
e2/e3 (%)	2.8	8.1	4.0	11.9	
e2/e4 (%)	2.8	27.0	9.3	14.9	
e3/e3 (%)	66.7	43.3	57.4	38.9	
e3/e4 (%)	16.7	16.2	20.0	20.8	
e4/e4 (%)	6.9	2.7	8.0	4.5	
Alleles					0.038
ApoE4 (%)	23.6	24.3	22.7	22.4	
ApoE3 (%)	69.4	55.5	69.3	53.7	
ApoE2 (%)	7.0	20.2	8.0	23.9	
Serum ApoE (mg/dL)	0.94 ± 0.35	0.76 ± 0.27	0.88 ± 0.22	0.67 ± 0.13	0.01
CES-D score	18.5 ± 7.6	14.1 ± 2.9	17.9 ± 3.1	13.7 ± 4.3	0.03
MMSE (%)					0.00
<24	63.9	39.2	30.7	7.5	
≥ 24	36.1	60.8	69.3	92.5	

Notes: Continuous variables are presented as means $\pm$ S.D, categorical variables as numbers with percentage. Differences in proportions were tested using Pearson chi-square test; differences in means were tested using analysis of variance and Student–Newman–Keuls (SNK) multiple comparisons.

ApoE4, apolipoprotein E-ε4; ApoE3, apolipoprotein E-ε3; ApoE2, apolipoprotein E-ε2; *N*, number; MMSE, the Mini-Mental State Exam; CES-D, the Center for Epidemiological Studies Depression; Group I, patients with depression under hemodialysis; Group II, patients without depression under hemodialysis; Group III, patients with depression under nondialytic treatment; Group IV, patients without depression under nondialytic treatment.

Table 3. Associations between distribution of ApoE alleles and depression analyzed by multi-nominal logistic regression models.

	Model[1]		Model[2]	
	ApoE2 (+)	ApoE4 (+)	ApoE2 (+)	ApoE4 (+)
Risk for dialysis and depression[a]				
OR (95%CI)[b]	0.31 (0.12–0.87)	1.01 (0.51–2.13)	0.35 (0.17–1.05)	0.97 (0.48–2.05)
p-Value	0.02	0.92	0.02	0.93
Risk for depression without dialysis[a]				
OR (95%CI)[b]	0.36 (0.15–1.01)	0.93 (0.43–1.95)	0.34 (0.13–0.96)	0.91 (0.41–1.97)
p-Value	0.03	0.67	0.04	0.65
Risk for no (dialysis and depression)[a]				
OR (95%CI)[b]	1.24 (0.58–2.74)	0.92 (0.41–1.96)	1.07 (0.51–2.59)	0.89 (0.40–1.88)
p-Value	0.45	0.52	0.53	0.49

Notes: Model[1] is adjusted for age and sex; Model[2] is adjusted for educational level, drinking and smoking history, vascular risk factors and cognitive function. OR, odds ratio; CI, confidence intervals.

[a]Dialysis without depression was as the control group (Group II).

[b]ApoE carrier status for negative (ApoE2(−) and ApoE4(−)) was as the control group; ApoE2(+), ApoE2 carrier status for positive; ApoE4(+), ApoE4 carrier status for positive.

ApoE-ε4-positive, irrespective of dialysis. The overall frequency of ApoE-ε4 was lower in the present study compared to previous studies. Such differences could be contributed much to the ethnicity of populations and genders, since depression might be more associated with ApoE-ε4 in women than in men[20] and the frequency of ApoE-ε4 in Western populations is also higher compared to Asian populations.[21,22]

Nonetheless, those with ApoE-ε4/ε4 might experience depression with a relative paucity of depressive symptoms compared to those without this allele,[23] which was also shown in our study (6.9% in Group I and 8.0 in Group III). However, the biological mechanisms revealing the modulating effect of ApoE-ε4 on depression are not fully explicit. As reported, ApoE-ε4 is correlated with depressive symptoms among older adults, but is moderated by neighborhood environmental factors.[24]

Moreover, it is controversial whether ApoE-ε2 has a protective effect on depression.[25] In the present study, the frequency of ApoE-ε2 in depressive subjects is only 7.5% ($10 + 12/72 + 75$), significantly lower than that in the non-depressive subjects (25.2%, $30 + 32/74 + 67$). The reasons are probably that ApoE-ε2 might reduce the incidence of depression and protect the Chinese population from depression,[26] and also may decrease the vulnerability to depressive symptoms. As it is well-known, lipid metabolism could be affected by the frequency of ApoE.[27,28] High-density lipoprotein (HDL) and ApoE-HDL linked to suppression of extracellular matrix (ECM) gene expression and arterial stiffening can reduce the incidence of cardiovascular events. As reported, the occurrence of depressive symptoms is inversely and linearly associated with HDL.[29] Moreover, ApoE-ε2 is more associated with HDL than ApoE-ε4. However, the exact relation between these conditions is unclear. The FINE study[19] suggests an inverse association between serum total cholesterol and depressive symptoms, but does not show any association of depressive symptoms

with ApoE genotype or lipoprotein fractions. Thereby, it is inferred that low cholesterol is a consequence rather than a cause of depressive symptoms. Also ApoE may be important in stabilizing neurons or in compensatory synaptogenesis in face of a number of probable risk factors. Thus, ApoE2 may act as a qualitative trait locus and delay the onset age of depression,[30] though the effect was significantly weakened by controlling relevant baseline characteristics ($p < 0.05$).

Moreover, the patients with depressive symptoms tend to show higher serum ApoE content than those without depressive symptoms ($p < 0.05$). The patients undergoing hemodialysis also tend to have a higher serum ApoE content compared with the patients without receiving hemodialysis (although not significantly). As it is well-known, malnutrition–inflammation–atherosclerosis (MIA) syndrome is not rare among HD patients. Recently, many authors try to investigate the connection between depression and inflammatory status in ESRD patients.[31] Meanwhile, the disorder of ApoE may be influenced by inflammatory cytokines in the dialysis population, though there is no difference in hsCRP between the two groups.[32]

A few limitations in the current study should be noted. First, although we assessed a broad range of depressive disorders, it is difficult to ascertain the specific causes and the type of depression within this sample. Second, we did not discuss about ApoE allele heterozygotes versus homozygotes, since there was a significant difference in the impact of one or more ApoE alleles on the risk for other conditions, such as AD. Third, we excluded vascular depression depending on MRI diagnosis combined with vascular risk factors. The diagnosis of VD is not clearly defined for non-elderly patients. Therefore, the patients without VD might have been heterogeneous, although it might exclude more patients with VD in our study. Another important limitation is our small cohort size. The last and the most important imperfection is the case-control study, which is not enough to find the causality or temporal relationship between the occurrence of depression and the frequencies of ApoE alleles.

Conclusions

No association between the frequency of ApoE-ε4 and the occurrence of depression was found in patients with or without receiving hemodialysis. Further efforts should focus on pathogenetic and etiological studies to elucidate the course and the neuropathology of different types of depression, and to find out if ApoE-ε2 acts as a protective factor in Chinese dialysis population since it might decrease the prevalence of depression and delay the onset age.

Declaration of interest

The authors declare that they have no competing interests. This material is based upon work funded by Guangzhou medical key subject construction project of China (2013–2015).

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