Interactions of Vascular Risk Factors and Apolipoprotein E4 on Geriatric Depression*

Hye-Young Park, M.D., Ph.D.,[1)] Jae-Min Kim, M.D., Ph.D.,[1)2)]
Il-Seon Shin, M.D., Ph.D.,[1)2)] Su-Jin Yang, M.D., Ph.D.,[1)2)]
Sung-Wan Kim, M.D., Ph.D.,[1)2)] Seon-Young Kim, M.D.,[1)]
Hee-Young Shin, M.D., Ph.D.,[2)3)] Jin-Sang Yoon, M.D., Ph.D.[1)2)3)]†

노년기 우울증에서 혈관성 위험인자와 아포지단백 E4의 상호작용*

박혜영[1)] · 김재민[1)2)] · 신일선[1)2)] · 양수진[1)2)] · 김성완[1)2)] · 김선영[1)] · 신희영[2)3)] · 윤진상[1)2)3)]†

ABSTRACT

Objective : Associations of vascular risk/disease or apolipoprotein E ε4(APOE4) with geriatric depression has been unclear at a population level. This study aimed to evaluate whether there would be interactions of vascular risk/disease and APOE4 on depression in a Korean elderly population.

Methods : 732 community residents aged 65 or over were assessed for depression(GMS), information on vascular risk/disease(reported stroke, transient ishemic attack, heart disease, hypertension, diabetes, smoking), examinations for vascular risk/disease(blood pressure, blood tests for glucose and lipid profiles, body size), APOE genotypes, demographic characteristics(age, gender, education), physical health, and cognitive function(MMSE).

Results : Previous stroke and lower level of high density lipoprotein(HDL) cholesterol were significantly associated with geriatric depression independent of demographic characteristics, physical illnesses, and cognitive function. These associations were statistically significant only in those with APOE4, although the interaction terms didn't reach to statistical significance.

Conclusion : Associations between vascular risk/disease and geriatric depression might be more prominent in those with APOE4. However further research would be needed to clarify this issue.

KEY WORDS : Stroke · Vascular risk · Apolipoprotein E · Depression · Elderly.

*The study was funded by a grant of the Korea Health 21 R & D, Ministry of Health and Welfare, Republic of Korea (A050113).

[1)]전남대학교 의과대학 정신과학교실
Department of Psychiatry, Chonnam National University Medical School, Gwangju, Korea
[2)]전남대학교병원 우울증 임상연구 센터
Depression Clinical Research Center, Chonnam National University Hospital, Gwangju, Korea
[3)]전남대학교병원 임상시험 센터
Clinical Trial Center, Chonnam National University Hospital, Gwangju, Korea
†교신저자 : 윤진상, 501-746 광주광역시 동구 학동 5
전화) (062) 220-6142, 전송) (062) 225-2351, E-mail) jsyoon@chonnam.ac.kr

Introduction

Cerebrovascular disease and its common risk factors such as hypertension, diabetes and dyslipidemia are hypothesized to associate with geriatric depression.[1] Apolipoprotein E ε4 (APOE4) has been associated with ischemic cerebrovascular disease,[2] deep white matter hyperintensities,[3] coronary heart disease,[4] and increased levels of total and low density lipoprotein (LDL) cholesterol.[5] APOE4 can be reasonably hypothesized to be a risk factor for geriatric depression, considering its associations with these vascular risk/disease. However, majority of studies failed to find the association between APOE4 and geriatric depression[6-8] with some exceptions.[9] It may also be postulated that there would be combined effects of vascular risk/disease and APOE4 on geriatric depression. Recently, a study found no associations between APOE4 and cholesterol level or depression in cross-sectional and longitudinal analyses in a biracial elderly community sample.[10] To our knowledge, there has been no study to investigate the combined effects of vascular risk/disease other than cholesterol level and APOE4 on geriatric depression.

This study aimed to evaluate whether there would be interactions of vascular risk/disease and APOE4 on depression in a Korean elderly population. It was hypothesized that any of various vascular risks/diseases might have combined effects with APOE4 on depression independent of other potential confounding factors such as demographic characteristics, physical illnesses, and cognitive function.

Methods

The present study was part of a community survey of late-life psychiatric morbidity carried out in Kwangju, South Korea in 2001, in collaboration with the 10/66 Dementia in Developing Countries Research Program.[11] Data were gathered using a structured questionnaire developed by the 10/66 Dementia in Developing Countries Research Group[11] unless specified. Details of this project have been reported elsewhere.[12]

1. Study population

Potential participants for this study were recruited from all inhabitants aged 65 or over recorded in national residents registration lists within two areas (one urban, one rural) of Kwangju, South Korea in 2001. The study was approved by Chonnam National University Hospital Review Board. After sending a letter explaining the purpose of study to all eligible older people, written informed consent was obtained from all participants.

2. Assessment procedures

This study was conducted in two phases : 1) Sixteen graduate-level research assistants, trained and supervised by the project psychiatrist, carried out home-based interviews with participants and their family members. This included the Geriatric Mental State Schedule (GMS) ; [13] the Korean version of the Mini-Mental State Examination (MMSE-K) ; [14] and information on vascular risk/disease, physical illnesses, and demographic characteristics ; 2) At a second interview (attempted in all participants), examinations for vascular risk/disease and blood tests for APOE genotypes were administered by two expert teams, consisting of a psychiatrist, a senior nurse, and a psychologist. At both stages, home visits were repeated on at least two occasions if no contact was made. The mean (SD) interval between the two interviews was 8.7 (5.4) days. People who completed the two interviews and the blood tests formed the sample for the analysis presented here.

3. Depression

A community version of the GMS (GMS B3) was used. Procedures on its translation and validation into Korean (GMS B3-K) has been described elsewhere.[15] By the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm, depression is rated as AGECAT 0 to 5. AGECAT 0 have no or negligible relevant symptomatology, 1 and 2 are considered to be subcases, and 3 to 5 are considered to be likely cases. In the analyses, a confidence level 3 or above was used to define case level depression.

4. Information on vascular risk/disease

Self-reported diagnoses of and treatment for stroke, transient ischemic attack (TIA), heart disease, hypertension and diabetes were recorded. For stroke, it was coded

only if clear history of sudden onset of unilateral paralysis, and/or loss of speech, and/or blindness lasting for at least 2 days. For detection of TIA, a question "Have you ever developed sudden weakness of a limb, loss of speech, or partial blindness which got better quickly, in less than one day? Doctors sometimes call these attacks TIAs" was administered. Smoking history(pack-years) and current smoking were ascertained as well.

5. Examinations for vascular risk/disease

Resting blood pressure(BP) was taken with an automatic sphygmomanometer on the left arm in the sitting position. The lower of two consecutive readings was used. Blood tests were conducted for glucose ; total-, high density lipoprotein(HDL)-, low density lipoprotein(LDL)-cholesterol, and triglycerides ; and APOE genotypes. Participants were instructed to be fasting, and blood sampling was performed during the mornings when possible. Height, weight, waist, and hip were measured.

6. Potential confounding variables for depression

Demographic data on age, gender, and education was obtained. A structured questionnaire was administered enquiring about 11 common health problems. The items required simple yes(1) or no(0) response, and the individual scores totalled to generate a summary scale. Cognitive function was evaluated by the MMSE-K, which has been specifically developed for older Korean populations, with revised items taking into account low educational attainment and high rates of illiteracy.[14)]

7. Statistical analysis

Characteristics on vascular risk/disease were compared according to APOE genotype(no vs. have E4) using t-tests or chi-square tests as appropriate. Characteristics on vascular risk/disease were compared again according to depression(no vs. have depression). The associations between vascular risk/disease and depression(p values <0.1 in the univariate analysis) were further analyzed using stepwise logistic or linear regression models to investigate confounding/mediation by the potential variables on demographic characteristics, number of physical illnesses, and scores on MMSE-K. Effect modification by APOE genotypes was investigated through stratified analyses and through likelihood ratio tests for interaction terms within regression models.

Results

1. Recruitment

Of 1566 inhabitants aged 65 or over identified from registration lists, 1204(77%) completed the first interview with research assistants. Of the remainder, contact could not be established with 195(12%), 71(5%) refused to participate, 55(4%) had no fixed abode, 28(2%) had changed address, and 9(1%) had died before the visit. No significant differences were observed in age(mean ages, 72.2 and 72.4 respectively) and gender ratio(58% and 62% female, respectively) between participants and non-participants. Of the participants to the first interview, 732(61%) participated in the second investigation with expert teams. Of non-participants at this stage, contact could not be established with 321(27%), 92 refused(8%), 4 had died in the interval(<1%) and data was missing for 55(5%). These participants were less educated than non-participants(mean(SD) years of education 3.4(4.2) and 4.0(4.4), respectively ; p=0.035), had more number of physical illnesses(mean(SD) numbers 2.3(1.8) and 2.0(1.7), respectively ; p=0.007), and had lower cognitive function(mean(SD) scores on MMSE-K 23.3 (5.0) and 24.3(5.1), respectively ; p=0.002). However, no significant differences were observed between the participants and non-participants in terms of age (mean(SD) ages, 72.8(5.8) and 72.2(6.3), respectively), gender(59% and 57% female respectively), and GMS depression(14% and 13% respectively)(all p values, all>0.07). The principal apparent reason for attrition was that contact could not be established because the person was repeatedly away from home at the time of research visits.

2. Characteristics of the sample

Of the 732 participants, 101(14%) were diagnosed as having GMS depression, and 132(18%) had APOE4. Fifty one subjects(7%) had a history of previous stroke ; and 103(14%) of TIA. Self reported diagnoses of heart disease, hypertension, and diabetes were detected in 152

(21%), 235(32%), and 82(11%) participants, respectively. Mean(SD) level of systolic BP was 146.9(26.6) mmHg, diastolic BP 87.8(22.2) mmHg ; blood glucose 105.9(52.8) mg/dL ; total cholesterol 175.6(34.9) mg/dL, HDL cholesterol 48.0(13.9) mg/dL, LDL cholesterol 97.3(32.1) mg/dL, triglycerides 152.3(85.3) mg/dL. Mean(SD) body mass index(BMI ; kg/m^2) was 22.6 (3.6). The mean(range) level of lifetime smoking was 11.9(0−118) pack-years, and 295(40%) were current smokers.

3. Comparison of characteristics according to APOE genotypes

The results are displayed in Table 1. No differences were found in GMS depression and number of physical illnesses according to APOE4. In terms of vascular risk/disease, TIA was significantly more frequently reported

Table 1. Comparison according to apolipoprotein E (APOE) genotypes

	No APOE4 (n=600)	Have APOE4 (n=132)	p*
Information on vascular risk/disease, number (%)			
Stroke	37 (6)	14 (11)	0.067
Transient ischemic attack	76 (13)	27 (21)	0.019
Heart disease	119 (20)	33 (25)	0.177
Hypertension	188 (31)	47 (36)	0.354
Diabetes	69 (11)	13 (10)	0.438
Current smoker	235 (40)	60 (47)	0.167
Examinations for vascular risk/disease, mean (standard deviation)			
Systolic blood pressure (mmHg)	147.0 (26.2)	146.3 (28.8)	0.771
Diastolic blood pressure (mmHg)	87.5 (22.0)	88.8 (23.3)	0.570
Blood glucose (mg/dl)	107.0 (54.4)	103.4 (44.5)	0.304
Total cholesterol (mg/dl)	174.7 (34.0)	179.9 (39.1)	0.143
High density lipoprotein cholesterol (mg/dl)	48.2 (13.9)	47.2 (13.7)	0.523
Low density lipoprotein cholesterol (mg/dl)	96.7 (31.8)	100.2 (33.5)	0.277
Triglyceride (mg/dl)	150.2 (80.5)	162.1 (104.9)	0.250
Body mass index (kg/m^2)	22.8 (3.5)	22.1 (3.6)	0.041
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)	0.204

* : χ^2-or t-tests

Table 2. Stratified analyses of the associations of depression with vascular risk/disease by apolipoprotein E (APOE) genotype. Data are odds ratios[a] or Bs[b] (95% confidence intervals)

	Total sample (n=732)	No APOE4 (n=600)	Have APOE4 (n=132)	p (inter-action)
Stroke[a]	2.58† (1.26−5.30)	2.04 (0.87−4.78)	8.29* (1.56−43.94)	0.193
Transient ischemic attack[a]	1.53 (0.88−2.66)	1.42 (0.74−2.72)	3.27 (0.90−11.91)	0.597
Heart disease[a]	1.49 (0.88−2.54)	1.43 (0.79−2.61)	1.79 (0.46− 6.91)	0.581
Hypertension[a]	1.09 (0.69−1.74)	1.03 (0.53−1.61)	1.57 (0.57− 2.82)	0.227
Diabetes[a]	1.68 (0.90−3.13)	1.60 (0.73−2.50)	1.74 (0.30−13.40)	0.551
High density lipoprotein cholesterol[b]	−4.52† (−7.66, −1.36)	−4.40 (−9.30, 0.74)	−4.83† (−12.54, −1.36)	0.486
Low density lipoprotein cholesterol[b]	5.82 (−1.16, 12.79)	3.78 (−3.76, 11.33)	18.18 (−0.49, 39.87)	0.460

All results are adjusted for age, gender, education, number of physical illnesses, and scores on Korean version of Mini-Mental State Examination. * : $p<0.05$, † : $p<0.01$

and BMI was significantly lower in those with APOE4. The association between reported stroke and APOE4 was bordered significance. However, there were no significant differences in all the other variables.

4. Univariate and multivariate associations with depression

Detailed results of these analyses have been published elsewhere.[12] In the univariate analyses, depression was significantly associated with reported stroke, TIA, heart disease, lower level of HDL and higher level of LDL cholesterol. Associations with reported hypertension and diabetes were bordered significance. In terms of other factors than vascular risk/disease, depression was significantly associated with female gender, higher number of physical illnesses, and lower scores on MMSE-K. Results of the multivariate regression analyses after adjustment for age, gender, education, number of physical illnesses and scores on MMSE-K revealed that the associations of depression with reported stroke and lower level of HDL cholesterol were remained significant, while those with TIA, heart disease, hypertension, diabetes, and higher level of LDL cholesterol lost significance.

5. Stratified analyses according to APOE4 status (Table 2)

Significant associations were observed between depression and reported stroke or lower level of HDL cholesterol only in those with APOE4, while the interaction terms didn't reach to statistical significance(p-values from likelihood ratio tests>0.1). Although the associations of depression with other vascular risk/disease were not statistically significant, they were consistently more prominent in those with have APOE4.

Discussion

In the present study, APOE4 was associated with TIA and stroke, consistent with a previous report.[16] In addition, APOE4 tended to associated with reported heart disease and hypertension, and higher levels of total and LDL cholesterol, also in keeping with previous reports.[4][5] Given the significant or potential associations of APOE4 with such vascular risk/disease, which have been known to associated with geriatric depression,[1][17] while APOE4 was not associated with depression in the present study, but which was consistent with the results that most studies have reported.[6-8]

The association between previous stroke and depression, observed in this population, has also been reported in other population-based studies.[18][19] In terms of the associations between lipid profiles and depression, no association was found between total cholesterol and depression, which was consistent with some reports,[10][20][21] but not with others that reported the association between low level of total cholesterol and depression.[22-24] Measurement of total cholesterol seemed to be spurious considering its composite profiles. Indeed, there have been previous reports that depression was associated with lower LDL cholesterol,[25] but was inversely associated with HDL cholesterol.[26] Our finding on an association of lower level of HDL cholesterol with depression was contradictory to some of previous reports. This might be due to racial difference, but cross-cultural studies would be needed to clarify it. The associations between other vascular risk/disease than stroke and HDL cholesterol and depression was less clear, and largely be accounted for by worse physical health and cognitive function. This observation was in keeping with previous population-based studies, which reported little evidence that vascular risk factors are an important cause of depression at a population level.[19][27][28]

To our knowledge, there has been no study to investigate the combined effects of vascular risk/disease other than cholesterol level and APOE4 on geriatric depression.[10] In this study, the associations of previous stroke and lower level of HDL cholesterol with depression were more prominent in those with APOE4. Although these interactions didn't reach significance, it might be plausible that there would be combined effects of vascular risk/disease and APOE4 on depression by the following reasons. i) Our finding showed that associations between vascular risk/disease and depression were more prominent in those with APOE4 in a consistent pattern. ; ii) There have been reports that APOE4 was associated with mortality.[16][29][30] Also depression in geriatric is associated with increased rates of mortality and institutionalization[31][32] as are vascular risk/disease. People with combinations of

these factors may therefore be under-represented in a cross-sectional community study. However these suggestions would be tentative, and prospective studies are required to clarify this issue.

One of the strengths of the study was that depression was ascertained using a widely validated diagnostic schedule, most other data were gathered using a structured questionnaire developed by the 10/66 Dementia Research Group.[11] In terms of sample representativeness, government registration lists represent a highly inclusive sampling frame for epidemiological research in South Korea since an accurate entry is required for many activities of daily living, including pension provision. However, the two stage selection processes reduced the representativeness of the participants compared to the source population. A large proportion of the identified population participated in the first phase interview, but an important degree of attrition occurred before the second phase interview due to limited resources for establishing contact within the time-frame of the survey. The participants were significantly less educated, and more likely to have physical illnesses and cognitive impairment, which might exaggerated the prevalence of vascular risk/disease and APOE genotypes. However, we feel it is unlikely that the observed associations are explained by recruitment bias.

Limitations of the study should also be considered. i) Age of onset for depression was not ascertained. ; ii) Differential institutionalization and mortalities, which were not investigated, could contribute to the prevalence bias. ; iii) Reporting bias is also possible although informant information was used where possible.

In conclusion, we found that i) previous stroke and lower level of HDL cholesterol were significantly associated with geriatric depression independent of demographic characteristics, physical illnesses, and cognitive function ; and ii) these associations were statistically significant only in those with APOE4. Public health measures and strategies might be to focus on this high risk group to prevent geriatric depression.

References

1. **Alexopoulos GS, Meyers BS, Young RC, Capbell S, Silbersweig D, Charlson M.** 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915-922.
2. **McCarron MO, Delong D, Alberts MJ.** APOE genotype as a risk factor for ischemic cerebrovascular disease. A meta-anaylsis. Neurology 1999;53:1308-1311.
3. **Nebes RD, Vora IJ, Meltzer CC, Fukui MB, Williams RL, Kamboh MI, et al.** Relationship of deep white matter hyperintensities and apolipoprotein E genotype to depressive symptoms in older adults without clinical depression. Am J Psychiatry 2001;158:878-884.
4. **Wilson PW, Schaefer EJ, Larson MG, Ordovas M.** Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol 1996;16:1250-1255.
5. **Smit M, de Knijff P, Rosseneu M, Bury J, Klasen E, Frants R, et al.** Apolipoprotein E polymorphism in the Netherlands and its effect on plasma lipid and apolipoprotein levels. Hum Genet 1988;80:287-292.
6. **Zubenko GS, Henderson R, Stiffler JS, Stabler S, Rosen J, Kaplan BB.** Association of the APOE ε4 allele with clinical subtypes of late life depression. Biol Psychiatry 1996;40:1008-1016.
7. **Mauricio M, O'Hara R, Yesavage JA, Friedman L, Kraemer HC, Van de Water M, et al.** A longitudinal study of apolipoprotein E genotype and depressive symptoms in community-dwelling older adults. Am J Geriatr Psychiatry 2000;8:196-200.
8. **Rigaud AS, Traykov L.** Apolipoprotein E ε4 allele and clinically defined vascular depression. Arch Gen Psychiatry 2002;59:290-291.
9. **Krishnan KRR, Tupler LA, Ritchif JC Jr, McDonald WM, Knight DL, Nemeroff CB, et al.** Apolipoprotein E ε4 frequency in geriatric depression. Biol Psychiatry 1996;40:69-71.
10. **Blazer DG, Burchett BB, Fillenbaum GG.** APOE ε4 and low cholesterol as risks for depression in a biracial elderly community sample. Am J Geriatr Psychiatry 2002;10:515-520.
11. **10/66 Dementia Research Group.** Dementia in developing countries. A consensus statement from the 10/66 Dementia Research Group. Int J Geriatr Psychiatry 2000;15:14-20.
12. **Kim JM, Stewart R, Shin IS, Yoon JS.** Vascular disease/risk and late-life Depression in a Korean community population. Br J Psychiatry 2004;185:102-107.
13. **Copeland JRM, Dewey ME, Griffiths-Jones HM.** A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. Psychol Med 1986;16:89-99.
14. **Park JH, Kwon YC.** Modification of the mini-mental state examination for use in the elderly in a non-western society: Part I. Development of Korean version of Mini-Mental State Examination. Int J Geriatr Psychiatry 1990;5:381-387.
15. **Kim JM, Stewart R, Prince M, Shin IS, Yoon JS.**

Diagnosing dementia in a developing country: an evaluation of the GMS-AGECAT algorithm in an older Korean population. Int J Geriatr Psychiatry 2003;18:331-336.
16. **McCarron MO, Weir CJ, Muir KW, Hoffmann KL, Graffagnino C, Nicoll JA, et al.** Effect of apolipoprotein E genotype on in-hospital mortality following intracerebral haemorrhage. Acta Neurol Scand 2003;107:106-109.
17. **Krishnan KRR.** Biological risk factors in late life depression. Biol Psychiatry 2002;52:185-192.
18. **Fuh JL, Liu HC, Wang SJ, Liu CY, Wang PN.** Poststroke depression among the Chinese elderly in a rural community. Stroke 1997;28:1126-1129.
19. **Stewart R, Prince M, Richards R, Brayne C, Mann A.** Stroke, vascular risk factors and depression. Cross-sectional study in a UK Caribbean-born population. Br J Psychiatry 2001;178:23-28.
20. **Brown SL, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ.** Low cholesterol concentrations and severe depressive symptoms in elderly people. BMJ 1994;308:1328-1332.
21. **McCallum J, Simons L, Simons J, Friedlander Y.** Low serum cholesterol is not associated with depression in the elderly: data from an Australian community study. Aust NZ J Med 1994;24:561-564.
22. **Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL.** Plasma cholesterol and depressive symptoms in older men. Lancet 1993;341:75-79.
23. **Partonen T, Haukka J, Virtamo J, Taylor PR, Lonnqvist J.** Association of low serum total cholesterol with major depression and suicide. Br J Psychiatry 1999;175:259-262.
24. **Steegmans PHA, Hoes AW, Bak AAA, Van der Does E, Grobbee DE.** Higher prevalence of depressive symptoms in middle-aged men with low serum cholesterol levels. Psychosom Med 2000;62:205-211.
25. **Aijanseppa S, Kivinen P, Helkala EL, Kivela SL, Tuomilehto J, Nissinen A.** Serum cholesterol and depressive symptoms in elderly Finnish men Int J Geriatr Psychiatry 2002;17:629-634.
26. **Horsten M, Wamala SP, Vingerhoets A, Orth-Gomer K.** Depressive symptoms, social support, and lipid profile in healthy middle-aged women. Psychosom Med 1997;59:521-528.
27. **Jones-Webb R, Jacobs DR Jr, Flack JM, Liu K.** Relationships between depressive symptoms, anxiety, alcohol consumption, and blood pressure: Results from the CARDIA Study. Alcohol Clin Exp Res 1996;20:420-427.
28. **Kim JM, Stewart R, Shin IS, Yoon JS.** Previous stroke but not vascular risk factors are associated with depression in a cognitively impaired older Korean population. Int J Geriatr Psychiatry 2002;17:453-458.
29. **Smith JD.** Apolipoprotein E4: An allele associated with many diseases. Ann Med 2000;32:118-127.
30. **Dal Forno G, Carson KA, Brookmeyer R, Troncoso J, Kawas CH, Brandt J.** APOE genotype and survival in mena and women with Alzheimer's disease. Neurology 2002;58:1045-1050.
31. **Brotady H, Harris L, Peters K, Hickie I, Boyce P, Mitchell P, et al.** Prognosis of depression in the elderly. Br J Psychiatry 1993;163:589-596.
32. **Bruce ML, Leaf PJ, Rozal GPM, Florio L, Hoff RA.** Psychiatric status and 9-year mortality data in the New Haven Epidemilogic Catchment Area Study. Am J Psychiatry 1994;151:716-721.