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Research report

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Abstract

Background: We aimed to examine differential effects of WMH on progression of depressive symptoms according to APOE ε4 status in the elderly.

Methods: We obtained data from elderly Korean subjects (n=707) aged 60 years or older at baseline from the CREDO study from November 2005 to July 2014. A linear mixed model stratified according to APOE genotype (APOE ε4 carrier vs. non-carrier) was constructed using GDS score as a primary outcome and degree of overall, deep, periventricular WMH evaluated by a visual rating scale as a risk factor of interest. We also tested interaction between APOE ε4, WMH and time as predictors of clinical progression on GDS scores to examine the moderating effect of APOE ε4 allele on the relationship between degree of WMH and progression of geriatric depressive symptoms.

Results: The mean (SD) follow-up duration of the participants was 2.0 (0.8) years. Among APOE ε4 carriers, a severe degree of overall and deep WMH, but not periventricular WMH, predicted progression of geriatric depressive symptoms (overall WMH: coefficient = 0.96, p = 0.010; deep WMH: 0.87, p = 0.016). There were significant interaction between APOE ε4, WMH and time as predictors of clinical progression on GDS scores to examine the moderating effect of APOE ε4 allele on the relationship between degree of WMH and progression of geriatric depressive symptoms.

Limitations: Only subjects seeking medical attention and with follow-up measurements were enrolled in this study. Specific location of WMH and use of antidepressant were uncontrolled.

Conclusions: Considering biological markers such as degree of WMH and APOE ε4 status may be clinically relevant to predicting progression of geriatric depressive symptoms.

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1. Introduction

While studies have shown post-stroke depression to be associated with acute cerebrovascular events involving in large cerebrovascular, suggestions of an association between depression and small-vessel ischemic changes, such as white matter hyperintensity (WMH), have only recently emerged (Kales et al., 2005). WMH is believed to lead to the progression of depressive symptoms by damaging subcortical structures and disrupting
frontal-subcortical circuits related to mood regulation (Alexopoulos et al., 1997b). As an interpretation thereof, Krishnan et al. (1997) proposed their MRI-defined vascular depression hypothesis to emphasize the clinical importance of WMH in late-onset depression.

Nevertheless, among the elderly, patients with severe WMH do not always exhibit depressive symptoms greater in severity than those in patients with mild WMH. Thus, differences in the effects of WMH on progression of depressive symptoms might be related to a genetic susceptibility thereto. Among various candidate genes, the ε4 allele of the apolipoprotein E (APOE) gene may account for this genetic predisposition (Carmelli et al., 1998; DeCarli et al., 1999). According to previous studies, the APOE ε4 allele poses an increased risk for ischemic cerebrovascular disease in the elderly (de Leeuw et al., 2004; Krishnan et al., 1996; McCarron et al., 1999). Therefore, ischemic cerebrovascular disease contributes to the aggravation of depressive symptoms in the elderly, then the APOE ε4 allele may play a role in the regulation thereof. However, relatively little is known about these potential associations.

Herein, we hypothesized that the presence of the APOE ε4 allele would mediate the effects of WMH on progression of depressive symptoms in the elderly. Accordingly, we conducted a longitudinal analysis to investigate the effects of overall, deep and periventricular WMH on changes in depressive symptoms over time between APOE ε4 carriers and APOE ε4 non-carriers. We also examined whether the interaction between degree of WMH and APOE ε4 status contribute to progression of geriatric depressive symptoms.

2. Methods

2.1. Participants

The Clinical Research Center for Dementia of South Korea (CREDOS) dataset was used in the current analyses. The CREDOS study is a nationwide multicenter study designed to assess the occurrence of and risk factors for cognitive deterioration in the elderly. The CREDOS study, registered on ClinicalTrials.gov (identifier: NCT 01198093), recruited subjects from 31 university-affiliated hospitals from November 2005 to July 2014. All participants and their caregivers underwent comprehensive medical, neurological, and psychiatric interviews by trained psychiatrists, neurologists, and neuropsychologists at out-patient clinics. Physical and neurological examinations; neuropsychological tests; MRI scans; laboratory investigations as well as the Clinical Evaluation Form developed by the CREDOS study were conducted at baseline and at each visit during the follow-up period. The subjects in the CREDOS study consisted solely of elderly subjects of Asian ethnicity. A more detailed description of the CREDOS study is available elsewhere (Son et al., 2012). Of 1478 participants with data available for degree of WMH, APOE genotype and Geriatric Depression Scale scores at baseline and the follow-up period, 707 patients who completed at least one follow-up visit were finally included in this study. Subjects met the following inclusion criteria: (1) age of 60 years or older and (2) at least one visit during the follow-up period after baseline examination. Our study’s exclusion criteria comprised a (1) history of hearing or visual impairment that would potentially hinder the interview process; (2) history of large-vessel cerebrovascular disease, such as territorial infarction, high signal abnormalities on MRI due to vasculitis, multiple sclerosis, or leukodystrophy, in order to limit the recruitment of participants to only those with small-vessel cerebrovascular disease as possible; (3) history of other neurologic disorders (e.g., intracranial hemorrhage, brain tumor, Parkinson’s disease, hydrocephalus, severe head trauma, and dementia); (4) history of depression before the age of 60 years; (5) history of severe psychiatric disorders or developmental disorder (e.g., schizophrenia, mental retardation, or mania); (6) history of psychoactive substance use; and (7) the presence of comorbid medical conditions, including respiratory disease, malignancy, and hepatic or renal disease. The mean duration of follow up was 2.0 years (standard deviation: 0.8, maximum follow-up: 6.1 years). Subjects who performed at least one follow-up clinical interview had a longer duration of education (t = –4.6, p = 0.001), lower baseline GDS score (t = 2.6, p = 0.008), and be older than those with did not (t = –3.7, p = 0.001). Baseline MMSE score between subjects who performed at least one follow-up and did not was not statistically significant (t = 1.3, p = 0.189). Subjects who underwent more than twice follow-up visits were relatively small (N = 257, 36.4%). In this study, subjects with who completed follow-up evaluation were only enrolled for longitudinal study, which explains the relatively low retention rate of the study. This study was approved by the Institutional Review Boards of the participating centers. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Measurements

2.2.1. Visual rating of white matter hyperintensity

Degree of WMH was evaluated according to the modified criteria proposed by Fazekas et al. (1987) and Scheltens et al. (1993) on T2-axial or fluid-attenuated inversion recovery images. WMH was examined separately for deep white matter and periventricular white matter hyperintensity lesions. The severity of DWMH lesions was classified according to the greatest diameter of the lesions as mild (deep white matter < 10 mm in diameter, D1), moderate (deep white matter from 10 mm to < 25 mm in diameter, D2), or severe (deep white matter ≥ 25 mm in diameter, D3). The severity of PVWMH lesions was categorized according to the sizes of their cap and band, which ran perpendicular and horizontal to lateral ventricles, respectively, as mild (cap and band < 5 mm, P1), moderate (cap and band from 5 mm to < 10 mm, P2), or severe (cap and band ≥ 10 mm, P3). The degrees of overall WMH were divided into one of three groups according to DWMH and PVWMH severity: mild (D1P1, D1P2), moderate (neither mild nor severe: D1P3, D2P1, D2P2, D2P3, D3P1, D3P2), or severe (D3P3). Intra-class correlation coefficients (ICCs) were conducted on the Fazekas/Scheltens classification by the CREDOS study central committee. The Kappa coefficients for WMH visual rating scale was good (κ = 0.726–0.905) (Noh et al., 2014).

2.2.2. APOE genotyping

Genomic DNA was extracted from venous blood samples at baseline. Blood samples from each individual were collected in EDTA tubes, and APOE genotype was determined using the polymerase chain reaction. We defined participants with e4/e4 homozygote or e3/e4 heterozygote as APOE ε4 carriers and those with e3/e3 alleles as APOE ε4 non-carriers. We excluded subjects with an APOE ε2 allele (APOE e2/e4, APOE e2/e3, or APOE e2/e2) due to inconsistent reports on its association with an increased risk for ischemic cerebrovascular disease and its relatively low frequency in the general population (McCarron et al., 1999; Steffens et al., 2003).

2.2.3. Evaluation of depressive symptoms

Depressive symptoms were assessed by the Korean version of the Geriatric Depression Scale (GDS)-Short Form, a self-report questionnaire validated for use in elderly Korean subjects (Bae and Cho, 2004). The questionnaire consists of 15 yes–no questions related to depression. A cut-off point of 8 exhibits a sensitivity of 85% and a specificity of 69% for diagnosing a major depressive episode, compared to the Diagnostic and Statistical Manual of
Table 1
Baseline characteristics of the participants according to the APOE ε4 allele and degree of WMH (N=707).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=707)</th>
<th>APOE ε4 carrier (N=384)</th>
<th>APOE ε4 non-carrier (N=323)</th>
<th>Degree of WMH</th>
<th>χ² or F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>71.3 ± 7.8</td>
<td>71.6 ± 6.6</td>
<td>71.0 ± 7.1</td>
<td>73.7 ± 7.1</td>
<td>8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.5 ± 3.2</td>
<td>12.8 ± 3.7</td>
<td>12.0 ± 3.3</td>
<td>12.2 ± 3.1</td>
<td>1.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking</td>
<td>49.4%</td>
<td>49.4%</td>
<td>49.4%</td>
<td>49.4%</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.2%</td>
<td>37.2%</td>
<td>37.2%</td>
<td>37.2%</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36.4%</td>
<td>36.4%</td>
<td>36.4%</td>
<td>36.4%</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>172.6 ± 31.0</td>
<td>172.6 ± 31.0</td>
<td>172.6 ± 31.0</td>
<td>172.6 ± 31.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>MMSE score</td>
<td>24.4 ± 4.6</td>
<td>24.1 ± 4.3</td>
<td>24.4 ± 4.3</td>
<td>24.4 ± 4.3</td>
<td>1.4</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Notes: WMH = White Matter Hyperintensity, MMSE = Korean version of the Mini-Mental State Examination, GDS = Geriatric Depression Scale.

The baseline characteristics of the participants were evaluated according to their degrees of WMH in relation to the presence of the APOE ε4 allele. Discrete and continuous variables were compared using ANOVA or chi-square tests. Data were analyzed using linear mixed models with a random intercept for each subject and an unstructured model correcting for within-subject correlation. We hypothesized that the slope or shape of the association between the degree of WMH and change in depressive symptoms would differ according to the presence of APOE ε4 allele. Therefore, we stratified total sample into APOE ε4 carrier and non-carriers at first, and then compared β coefficients and their 95% confidence intervals for the GDS scores in linear mixed model for each strata to determine whether there was evidence of differential effect of degree of WMH and time on progression of geriatric depressive symptoms according to APOE ε4 status. We also considered a statistical model to calculate interaction term for APOE ε4*WMH*time to explore the modifying effect of APOE ε4 allele on the association between degree of WMH and progression of geriatric depressive symptoms. Linear mixed effects models tested interaction between APOE ε4, WMH and time as predictors of clinical progression on the Geriatric Depression Scale (GDS). The linear mixed model was fitted by considering subjects as random effects and time, degree of WMH, APOE ε4 status and interactions of degrees of WMH, APOE ε4 status and time as fixed effects. We performed identical statistical analyses for the pessimism, mood, and motivation subscales of the GDS instead of total GDS score. All values of p < 0.05 were considered statistically significant. SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

3. Results

Baseline demographic and clinical characteristics of the study participants according to degree of WMH between APOE ε4 carriers and APOE ε4 non-carriers are shown in Table 1. The mean follow-up duration among the participants was 2.0 ± 0.8 years. Of the 707 participants, 261 (36.9%) were male and 446 (63.1%) were female; the male to female ratio was approximately 1:2. The mean age of the participants was 71.3 ± 7.8 years, and the mean number of years of education was 9.0 ± 5.2 years. The average MMSE score...
was 24.4 ± 4.6, which was higher than the cutoff for potential dementia, 17/18 (Kim et al., 2002). The distribution of APOE genotype among the 707 subjects was as follows: 60 were APOE ε4 carriers, 323 were APOE ε3/ε4, 263 were APOE ε3/ε3, and 384 were APOE ε4 non-carriers. APOE ε4 carriers comprised 54.3% (n = 384) of the total study population, while APOE ε4 carriers encompassed 45.7% (n = 323). According to degree of WMH, it showed statistical differences in age and HTN. Four variables that approached conventional levels of significance comparing between APOE ε4 carrier and non-carrier were age, sex, education, and MMSE. There were no statistical differences in mean GDS score at baseline according to degree of WMH in both APOE ε4 carriers and non-carriers (Table 2). But, when we observed mean GDS scores in last follow-up visit among APOE ε4 carriers, tendency to complaining of severe depressive symptoms in subjects with severe WMH were more apparent than those with mild WMH (mild: 4.8 ± 3.9 vs. severe: 6.3 ± 4.2, p = 0.088 using multiple comparisons in ANOVA) even though mean follow up periods were not statistically different between two groups (mild: 2.0 ± 1.0 years vs severe: 1.9 ± 0.9 years, p = 0.661 using multiple comparisons in ANOVA). And it seemed to be similar to non-carriers (Table 2). Fig. 1 also revealed changes in depressive symptoms according to degree of WMH in each APOE ε4 strata. Because all 707 participants have both a baseline and first follow-up visit data at least, we compared mean changes in GDS score between baseline and first follow-up measurement to examine progression of geriatric depressive symptoms according to degree of WMH in each APOE ε4 strata. As a result, APOE ε4 carriers with severe WMH presented higher changes in GDS scores compared to those with mild WMH whereas non-carriers with severe WMH did not. Table 3 showed longitudinal associations between degree of WMH and progression of geriatric depressive symptoms in each strata of APOE ε4 status. Among APOE ε4 carriers, the linear mixed model analyses showed that severe WMH predicted progression of depressive symptoms, compared to mild WMH (coefficient for GDS scores [95% CI]; 1.10 [0.39, 1.81]; p = 0.010), after adjusting for age at baseline, sex, and years of education (Model 1). Adjustment for the confounding effects of vascular burden and cognitive burden (Models 2 and 3) did not change the overall outcomes (Model 3: 1.10 [0.37, 1.83]; p = 0.003). Meanwhile, these associations were not statistically significant among APOE ε4 non-carriers (0.29 [−0.15, 0.73]; p = 0.198). There were no main effect of APOE ε4 status on progression of geriatric depressive symptoms (F = 2.61, p = 0.107). However, there were significant interactions between APOE ε4 status, degree of WMH and time in predicting GDS score increase (F = 2.28, p = 0.046). These results suggested a modifying effect of APOE ε4 allele on the progression of geriatric depressive symptoms associated with degree of WMH.

We examined the effect of DWMH severity on progression of depressive symptoms in each APOE ε4 strata (Table 4). As in the results for overall WMH, severe DWMH was associated with the aggravation of depressive symptoms, compared to mild DWMH, in APOE ε4 carriers (1.00 [0.30, 1.70]; p = 0.005), but not in APOE ε4 non-carriers (0.31 [−0.12, 0.73]; p = 0.159). Notwithstanding, this finding was not replicated for PVWMH: severe PVWMH was not predictive of longitudinal changes in depressive symptoms during follow-up for either APOE ε4 carriers (0.46 [−0.05, 0.98]; p = 0.080) or non-carriers (0.42 [−0.08, 0.83]; p = 0.094).

In addition to total GDS score, we also investigated the relationships between degree of WMH and subscales of the GDS (pessimism, mood, and motivation) in each APOE ε4 strata. In longitudinal analysis of overall WMH, severe WMH, compared to mild WMH, showed positive associations with the pessimism subscale (0.59 [0.22, 0.97]; p = 0.002) and motivation subscale (0.26 [0.02, 0.50]; p = 0.037) in APOE ε4 carriers after adjusting...
covariates. Meanwhile, no significant effects on the pessimism, mood, and motivation subscales were noted for severe WMH among APOE ε4 non-carriers. As above, we also conducted linear mixed model analysis for DWMH and PVWMH. Severe DWMH was associated with increases in pessimism ($0.54 \pm 0.18, 0.91$; $p = 0.003$) and motivation subscale scores ($0.24 \pm 0.01, 0.47$; $p = 0.041$) over time in APOE ε4 carriers, whereas severe PVWMH was not predictive for any subscales of the GDS (Table 4).

### 4. Discussion

In the present study, among APOE ε4 carriers, those with severe WMH presented with more depressive symptoms over time than those with mild WMH. This was not observed in APOE ε4 non-carriers. Moreover, these results remained unchanged after controlling for demographic factors, vascular risk factors and MMSE. Although the role of WMH on depressive symptoms among geriatric patients has been mentioned in several studies (Wang et al., 2014), our results suggested that the APOE ε4 allele could regulate the effects of WMH on the progression of depressive symptoms in the elderly.

In the literature, a few studies have shown the APOE ε4 allele and WMH to be factors contributing to depressive symptoms in the elderly. A cross-sectional study by Nebes et al. examined the relationship between severe WMH and depressive symptoms in 92 community dwelling elderly subjects, and found that the relationship between severe WMH and depressive symptoms was especially strong in subjects with the APOE ε4 allele (Nebes et al., 2001). Lavarasky et al. conducted a longitudinal observational study on 16 elderly patients with depression for 6 years and reported that the presence of either the ApoE ε4 allele (Nebes et al., 2001). Lavarasky et al. conducted a longitudinal observational study on 16 elderly patients with depression for 6 years and reported that the presence of either the ApoE ε4 allele and WMH to be factors contributing to depressive symptoms in the elderly.
associated with a higher number of depressive episodes and lower mean age at depression onset (Lavretsky et al., 2000). They further suggested that the presence of the APOE ε4 allele might pose a risk for an increase in WMH size over time, thereby leading to the development of chronic depression. Despite inter-study heterogeneity in methodology and sample size, the overall results of these two studies corroborate those of the present study: severe WMH is associated with the aggravation of depressive symptoms over time in elderly subjects carrying the APOE ε4 allele.

Although the pathophysiology of the APOE ε4 allele in regulating the effects of WMH on depressive symptoms is unclear, it might be associated with the process of neuronal repair post-ischemia. Reportedly, the main role of astrocyte-derived APOE in the brain is to transport lipid components important to myelin sheath construction (Dik et al., 2001; Mahley, 1988). Among subjects of differing APOE genotype, those with the APOE ε4 allele have been shown to exhibit impaired neuronal repair, particularly abnormal dendrite formation and synaptogenesis. V. Heise et al. demonstrated that the APOE ε4 allele has a negative effect on brain white matter integrity that is evident even in early adulthood and remains relatively stable throughout adulthood (Heise et al., 2011). Accordingly, we suspect that carriers of the APOE ε4 allele who experience ischemia-induced white matter lesions in areas related to mood regulation may suffer from delayed recovery of white matter integrity due to impaired neuronal repair, thereby further accelerating the progression of depressive symptoms. In other words, the APOE ε4 allele might amplify the negative effects of severe WMH on the development of depressive symptoms by impairing repair mechanisms and poses an increased susceptibility to brain injury (DeCarli et al., 1999).

Vascular depression is reportedly associated with a lack of motivation (Alexopoulos et al., 1997a). Previously, Nebes et al. (2001) who examined the effects of WMH and the APOE ε4 allele on depressive symptoms, reported that a lack of motivation was predominant among subjects with severe WMH and APOE ε4 allele. As in previous studies, our study also noted a longitudinal relationship between WMH and the motivational subscale of the GDS among APOE ε4 carriers. Pessimism was also associated with depressive symptoms in longitudinal analysis, while mood was not. In consideration thereof, we tentatively concluded that cognitive domains of depressive symptoms, as reflected on the motivation and pessimism subscales, are more affected by WMH than mood among APOE ε4 carriers. However, this should be interpreted with caution because motivational symptoms of GDS might be somewhat distinct from the concept of apathy related to frontal-striatal dysfunction (Alexopoulos et al., 1997a; O’Brien and Ames, 1996). The motivational subscale of GDS is a subjective evaluation of the individual patient’s own motivational status. Therefore we might explain that patients with severe WMH are more likely to complain of a greater lack of motivation and pessimism than fluctuations in mood.

4.1. Limitations

This study had some limitations. First, since the subjects who participated in this study were enrolled after seeking medical attention, recall and selection bias might have been present. In addition, we analyzed only subjects who performed at least one follow-up measurement except baseline examination. Hence, the results of this study may not be easily generalized to other elderly populations. Second, we did not consider the specific locations of WMHs according to lobes, which could have influenced the severity and expression of depressive symptoms. This study was also only focused on WMHs rather than other small-vessel cerebrovascular disease such as lacunar infarction. Third, we did not control for the use of psychotropic drugs, including antidepressants, or duration and frequency of depressive episodes after first onset. Fourth, there might have been substantial inter-group heterogeneity, such as preclinical Alzheimer’s disease. One could plausibly suggest that depressive symptoms in subjects with severe WMH and APOE ε4 allele reflect the presence of preclinical Alzheimer’s disease. However, we tried to decrease the influence of dementia statistically by excluding definitely demented patients and also by adjusting for MMSE score in this study.

5. Conclusions

In conclusion, this study demonstrated that APOE ε4 carriers with severe overall WMH experience more depressive symptoms over time than those with mild WMH. Considering WMH and presence of the APOE ε4 allele may be clinically relevant to predicting aggravation of depressive symptoms in geriatric patients, especially presenting motivational problem or pessimism.

Role of funding source

The funding agency had no influence on design of the study or interpretation of results.

Conflicts of interest

No disclosures to report.

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