International Psychogeriatrics (2019), 31:1, 101–108 © International Psychogeriatric Association 2018
doi:10.1017/S1041610218000558

Increased plasma complement factor H is associated with geriatric depression

Cheolmin Shin,[1] Byung-Joo Ham,[1] Young-Hoon Ko,[1] Chi-Un Pae,[2] Moon Ho Park,[3] David C. Steffens,[4] Ashwin A. Patkar[5] and Changsu Han[1]

[1]*Department of Psychiatry, College of Medicine, Korea University, Seoul, Republic of Korea*
[2]*Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[3]*Department of Neurology, College of Medicine, Korea University, Seoul, Republic of Korea*
[4]*Department of Psychiatry, University of Connecticut Health Center, Farmington, Connecticut, USA*
[5]*Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, North Carolina, USA*

ABSTRACT

Background: Complement factor H (CFH) plays a key role in regulating the cascade of the alternative pathway of the complement system. Dysregulation of CFH may be involved in the pathophysiology of various inflammation-mediated diseases including neuropsychiatric illnesses. This study aimed to investigate this relationship by examining determining CFH levels in elderly individuals with and without depression.

Methods: A total of 152 elderly individuals (major depressive disorder (MDD) group, $n = 76$; comparison sample, $n = 76$) were selected from the Ansan Geriatric study. The plasma level of CFH was measured. MDD was diagnosed with the Mini-International Neuropsychiatric Interview as per DSM-IV criteria. The severity of depression was evaluated with the geriatric depression scale (GDS). Mean CFH levels were compared using the Mann–Whitney *U* test. After adjusting for possible confounding factors including age, sex, marital status, education, alcohol use, hemoglobin levels, and the Korean version of the Mini-Mental State Examination (MMSE-KC), a multiple regression analysis was conducted. The GDS score and plasma level of CFH were analyzed using Spearman's correlation.

Results: Plasma CFH level was significantly higher in individuals with MDD than in the comparison sample (289.51 ± 21.16 vs. 339.67 ± 66.23, $p < 0.001$). In a regression model adjusted for possible confounders, CFH was significantly associated with geriatric depression ($p < 0.001$). CFH levels were not significantly related to GDS scores in the depressed group.

Conclusion: This study revealed an association between high plasma levels of CFH and geriatric depression, thereby suggesting the alternative pathway of the complement system contributing to the development of geriatric depression.

Key words: complement factor H, geriatric depression, complement system, alternative pathway

Introduction

Aging-related inflammation is considered to be involved in the onset of late-life depression (Bruunsgaard *et al.*, 2001). Owing to abnormalities in the regulation of the immune system during aging, excessive innate immune responses ensue (Gruver *et al.*, 2007). This may lead to a pro-inflammatory state throughout the whole body, and cause imbalances in the immune activity of the central nervous system (Dilger and Johnson, 2008). Previous studies revealed that the increase of immune substances such as interleukin-1beta and interleukin-6 were associated with geriatric depression (Thomas *et al.*, 2005; Bremmer *et al.*, 2008).

The complement system mediates an important immune response between the innate and acquired immune systems, leading to the initiation of various immune regulation processes. Under normal conditions, the complement system undergoes a series of cascades to generate complements and multiple immune substances, mediating a variety of inflammatory responses against the

Correspondence should be addressed to: Changsu Han, MD, PhD, MHS, Department of Psychiatry, College of Medicine, Korea University, Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do 15355 Seoul, Republic of Korea. Phone: +82-31-4125140; Fax: +82-31-4125144. Email: hancs@korea.ac.kr. Received 16 Oct 2017; revision requested 18 Nov 2017; revised version received 6 Mar 2018; accepted 9 Mar 2018. First published online 25 May 2018.

antigen. Therefore, it has been considered that abnormalities in the normal control function of the complement system may contribute to the pathophysiology of various diseases mediated by inflammation (Gasque *et al.*, 2000; de Cordoba *et al.*, 2012).

Complement factor H (CFH) is a glycoprotein in the serum that regulates the cascade of the complement system in the alternative pathway by inhibiting the formation and function of complement component 3 (C3) and complement component 5 (Zipfel *et al.*, 1999). CFH is synthesized in the liver and is normally present at concentrations of about 250–270 mg/L in the serum (Hakobyan *et al.*, 2008). When a CFH-deficient state occurs in the body, the complement system activity is increased, leading to a chronic inflammatory reaction that damages host cells by autoimmunity (Rodriguez de Cordoba *et al.*, 2004). The inflammatory response induced by CFH dysregulation is believed to cause neuronal death, affecting neurodegeneration. Therefore, the elderly studies on CFH are mainly about neurodegenerative diseases such as Alzheimer's disease (AD), but the results have been inconsistent (Hye *et al.*, 2006; Hamilton *et al.*, 2007). One recent observational study reported the association between depression and CFH in depressed patients (Zhang *et al.*, 2016). In this study, plasma levels of CFH were lower in the depressed group than in the normal group, and specific polymorphism of the CFH gene was associated with depression.

Despite the evidence that CFH is involved in inflammation in the elderly, there is no study investigating the relationship between geriatric depression and CFH. In the present study, it was assumed that there would be a decrease of CFH in the same context as the inflammatory hypothesis of geriatric depression. In order to test this, we investigated the differences in CFH, the constituents of the alternative pathway of the complement system, between patients with depression and healthy comparison sample.

Methods

Study population

The participants were recruited from the Ansan Geriatric (AGE) cohort study in 2003. The AGE study was a prospective population-based cohort study aiming to investigate the prevalence, incidence, and associated risk factors of geriatric diseases such as dementia, geriatric depression, and metabolic syndrome and to collect comprehensive information on the overall health and functional status of the elderly population, conducted in Ansan-si city in the province of Gyeonggi-do, South Korea. The detailed process of the sampling protocol and research design of the AGE study have been reported in several studies (Kim *et al.*, 2007; Han *et al.*, 2009). A total of 2,767 individuals were selected as the baseline sample to represent the target population, following a screening procedure that excluded non-eligible participants. In the first wave of the study, 1,391 participants (595 men and 796 women) were randomly selected from September 2004 to March 2006. This sample was evaluated through clinical and neuropsychological examinations at the Geriatric Health Clinic Research Institute of Korea University Ansan Hospital. All data used in this study were obtained from the first wave of the study.

Of the 1,391 participants, 777 were assessed, using the Korean version of the Mini-International Neuropsychiatric Interview (MINI) (Yoo *et al.*, 2006), administered by a trained clinical psychologist and a psychiatrist. A final research diagnosis of major depression was derived, based on a consensus meeting of the psychiatrist, clinical psychologist, and a neurologist. As a result, the number of persons classified as non-depressed, and included in the comparison sample, and depressed subjects in the cohort were 653 and 124, respectively. Among them, 76 non-depressed individuals in the comparison sample and 76 depressed subjects were allocated by simple random sampling. This sample size was considered sufficient to test the association between depression and control considering the following conditions: medium standard effect size of 0.5, the significance level of 0.05, and the power of 0.85 (Cohen, 1992). Since the CFH estimates have not been determined by previous studies, Cohen's method was used.

Evaluation of depression severity and cognition

Depressive symptoms were assessed in accordance with the Korean version of the 30-item GDS (GDS-K). The GDS is a self-reported scale used for the assessment of depression in the elderly population. The GDS-K has been modified, supplemented, and standardized several times, showing high sensitivity and specificity (Jung *et al.*, 1997; Bae and Cho, 2004).

To evaluate overall cognitive function, the Korean version of the Mini-Mental State Examination (MMSE-KC) as a part of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery of tests (CERAD-K) was utilized (Lee *et al.*, 2002).

Sociodemographic and clinical data

Sociodemographic and health-related data were collected at baseline and at each follow-up wave. Detailed data on sociodemographic and health-related factors such as age, sex, education level, marital status, smoking, alcohol consumption, medical history, and dietary supplementation were collected. Marital status was categorized as being married, living with a partner, and living alone. Smoking status was categorized as current smoker, ex-smoker, and non-smoker. The education level was classified into under 6 years (elementary school), 7–12 years (middle and high school), and over 13 years (college education level) based on the system of formal Korean education. The history of medical disease was reported by the participants using a checklist that included four categories of disease and a residual category called "other disease group," and the use of drugs, including antidepressants and anti-inflammatories, was also noted.

Laboratory procedure and analysis

Baseline blood samples were taken from September 2004 to March 2006, when the first wave of the AGE study was conducted. Through the venipuncture method, blood samples were collected after overnight fasting (12–14 h). These laboratory analyses were determined using commercially available kits. In particular, blood samples for immunoassay were collected in ethylenediaminetetraacetic acid tubes and centrifuged (within 4 h of collection) at 3000 rpm in for 10 min. Until the analysis, the blood samples were stored at −70 °C.

A multiplexing kit was purchased from Merck Millipore. In November 2014, blood was analyzed by multiplexing with Milliplex^{TM} Map Human neurodegenerative panel 1 using Luminex Instruments (Luminex Corporation, Austin, TX). The immunoassay kit measured α2-macroglobulin, apolipoprotein AI, apolipoprotein CIII, apolipoprotein E, C3, prealbumin, and CFH. Each plasma samples was measured single according to the manufacturer's protocols. According to the manufacturer's precision of the assay was reported that the intra-assay coefficients of variation were 5.0% for α2-macroglobulin, 5.8% for apolipoprotein AI, 5.7% for apolipoprotein CIII, 5.9% for apolipoprotein E, 3.3% for C3, 5.3% for prealbumin, and 2.6% for CFH. The inter-assay coefficients of variation reported by manufacturer were 8.0% for α2-macroglobulin, 16.6% for apolipoprotein AI, 16.6% for apolipoprotein CIII, 13.7% for apolipoprotein E, 9.9% for C3, 12.1% for prealbumin, and 11.2% for CFH. The plate was analyzed with xMAP Technology.

Ethics

All procedures related to the AGE study were conducted in accordance with the institutional guidelines. Written informed consent was provided by all participants. The study protocol was approved by the institutional review board of the Korea University Ansan Hospital.

Statistical analysis

Data are presented as means and standard deviations (continuous variables), or as frequencies and percentages (nominal variables). Among the variables evaluated in the depressed and control groups, categorical variables were assessed using the χ^2 test, and continuous variables were assessed using Student's *t*-test. The Mann–Whitney *U* test was used for variables that markedly violated the assumptions of the parametric *t*-test. The significant variables ($p < 0.2$) from the χ^2 test, *t*-test, and Mann–Whitney *U* test were considered as possible confounders and inserted into the logistic regression model. A logistic regression analysis was performed for the depression and comparison groups to adjust for the possible confounding variables. To investigate the correlation between depression severity and the inflammatory marker, we used Spearman's correlation to measure GDS scores and CFH. All data were analyzed using SPSS 20.0 for windows (SPSS, Inc., Chicago, IL). Statistical significance for the logistic regression model was set at $p < 0.05$.

Results

The characteristics of participants

A total of 152 participants were included in the study: 76 in the depressed group and 76 in the control group. The mean age of the control group was 66.17 ± 3.75 years and of the depressed group was 68.05 ± 4.90 years. The control group comprised 33 men and 43 women, and the depressed group comprised 16 men and 60 women. Smoking, BMI, heart disease, hypertension, and non-steroidal anti-inflammatory drugs (NSAIDs) were not significantly different between the depressed and control groups. The p values of alcohol consumption, MMSE-KC score, endocrine disease, and hemoglobin level were lower than 0.2. These variables were inserted into the logistic regression model. The detailed demographic characteristics and blood test results of the participants are shown in Table 1.

Comparison of mean plasma markers

The difference of mean of plasma CFH level between the depressed group (339.67 ± 66.23)

Table 1. Sociodemographic data of the study groups

	MDD ($N = 76$)	CONTROL ($N = 76$)	TEST STATISTIC	P VALUE
Age	68.05 (0.56)	66.17 (0.43)	$Z = -2.46$	0.014[c]
Women, *n* (%)	60 (78.9)	43 (56.6)	$\chi^2 = 8.70$	0.005[b]
Married or living with a partner, *n* (%)	48 (63.2)	63 (82.9)	$\chi^2 = 7.52$	0.006[b]
Smoking, *n* (%)				
Current	55 (72.4)	50 (65.8)	$\chi^2 = 2.73$	0.256[b]
Ex-smoker	14 (18.4)	12 (15.8)		
Non-smoker	7 (9.2)	14 (18.4)		
Education, *n* (%)				
≤6	52 (70.8)	28 (31.0)	$\chi^2 = 17.39$	<0.001[b]
7–12	21 (25.0)	34 (37.9)		
≥13	3 (4.2)	14 (31.0)		
Alcohol use, *n* (%), ≥ 3 times per week	9 (11.8)	19 (25.0)	$\chi^2 = 4.38$	0.036[b]
BMI, kg/m^2	25.05 (0.34)	24.95 (0.40)	$t = -0.20$	0.845[a]
GDS score	18.03 (0.66)	6.38 (0.55)	$Z = -9.15$	<0.001[c]
MMSE-KC	23.89 (0.55)	26.95 (0.26)	$Z = -4.55$	<0.001[c]
Endocrine disease, *n* (%)	37 (48.7)	26 (34.2)	$\chi^2 = 3.28$	0.070[b]
Cardiac disease, *n* (%)	17 (22.4)	15 (19.7)	$\chi^2 = 0.16$	0.691[b]
Hypertension, *n* (%)	32 (42.1)	27 (35.5)	$\chi^2 = 0.69$	0.405[b]
Use of NSAIDs, *n* (%)	14 (18.4)	9 (11.8)	$\chi^2 = 1.28$	0.258[b]
Hb (g/dL)	13.03 (0.14)	13.48 (0.14)	$t = 2.22$	0.028[a]
WBC ($\times 10^3/\mu$l)	5.86 (0.19)	5.87 (0.19)	$t = 0.04$	0.970[a]
TSH (μIU/mL)	1.92 (0.21)	1.89 (0.16)	$t = -0.09$	0.927[a]
CFH (μg/mL)	339.67 (7.60)	289.51 (2.66)	$Z = -5.41$	<0.001[c]
C3 (μg/mL)	171.09 (7.76)	172.04 (5.42)	$Z = -0.328$	0.743[c]
Prealbumin (μg/mL)	230.06 (6.95)	227.91 (5.78)	$Z = -0.212$	0.832[c]
α2-Macroglobulin (μg/mL)	1252.04 (31.80)	1201.21 (27.43)	$Z = -1.22$	0.223[c]
Apolipoprotein AI (μg/mL)	1595.08 (41.26)	1487.63 (35.63)	$Z = -1.819$	0.069[c]
Apolipoprotein CIII (μg/mL)	249.32 (11.51)	234.22 (11.02)	$Z = -1.220$	0.223[c]
Apolipoprotein E (μg/mL)	88.55 (2.87)	90.62 (3.18)	$Z = -0.013$	0.990[c]

Values are means unless otherwise mentioned (SE: standard error).
Abbreviations: MDD, major depressive disorder; BMI, body mass index; GDS, geriatric depression scale; MMSE-KC, Korean version of the Mini-Mental State Examination; NSAIDs, non-steroidal anti-inflammatory drugs; Hb, hemoglobin; WBC, white blood cells; TSH, thyroid-stimulating hormone; CFH, complement factor H; C3, complement component 3.
[a]Student's *t*-test.
[b]χ^2 test.
[c]Mann–Whitney *U* test.

and control group (289.51 ± 23.16) was significant (Figure 1).

Correlation between severity of depression and CFH concentration in the depressed group

Spearman's correlation was used to examine the relationship between GDS scores assessing the severity of depressive symptoms and the plasma levels of CFH in depressed group. CFH levels were not statistically significant with GDS scores, and Spearman's *r* coefficient was 0.08.

Multivariate regression model

Variables with a p value of less than 0.2 among the independent variables and the CFH variable were included in a multivariate binary logistic regression model for the depressed and control groups (Table 2). After adjusting for confounding variables, CFH was significantly associated with greater odds of depression, with an odds ratio of 1.03 (95% CI 1.02–1.05).

Table 2. Multivariable logistic regression model of the association between complement factor H and major depressive disorder ($n = 152$)

	WALD	P VALUE	ODDS RATIO (95% CI)
Complement factor H	16.79	<0.001	1.03 (1.02–1.05)

Adjusted for age, gender, married or living with a partner, education, alcohol use, hemoglobin level, and MMSE-KC.

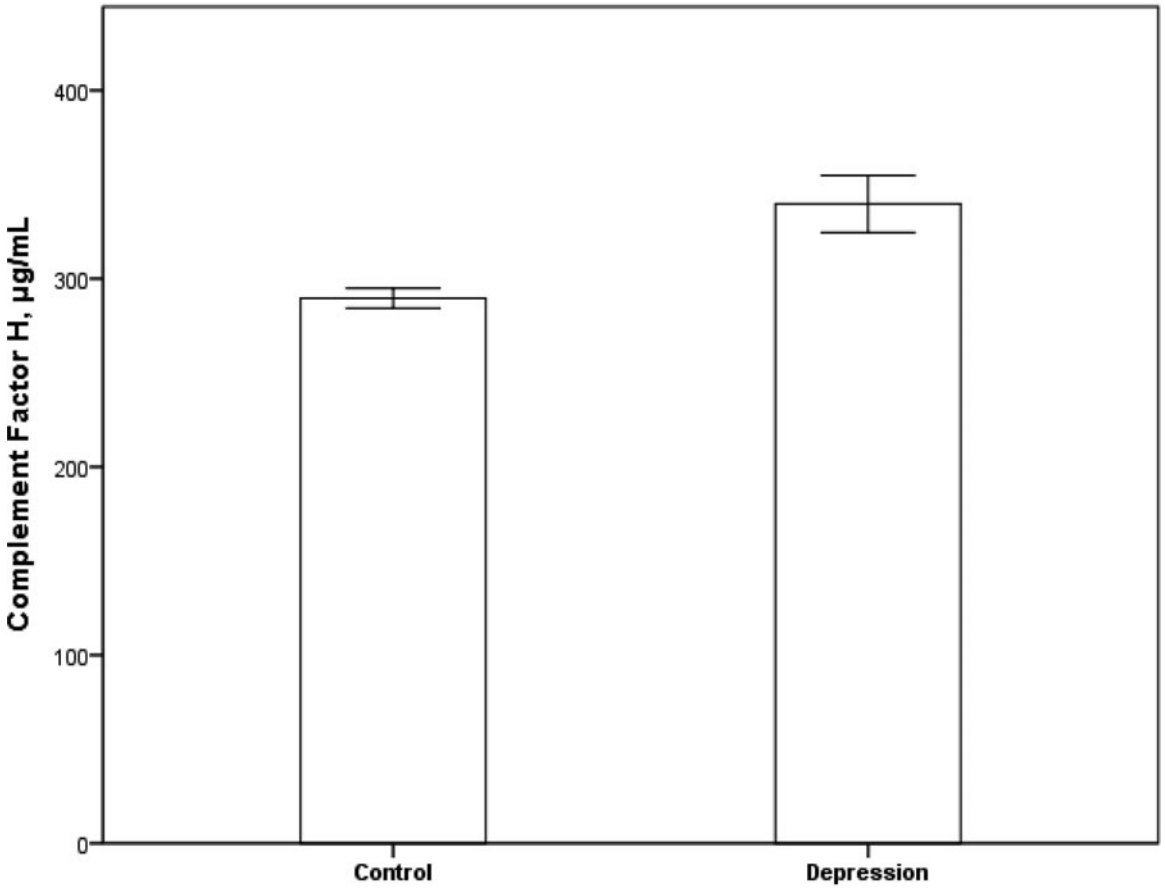

Figure 1. Distribution of the mean values of complement factor H in the study groups. Significant differences were observed between the control and depression groups ($p < 0.001$).

Discussion

The purpose of this study was to investigate the difference in a specific plasma inflammatory factor between non-depressed and depressed subjects. To our knowledge, this is the first report of higher plasma CFH levels in older depressed individuals. The main finding of this study was that the CFH plasma levels were significantly higher in the depressed group than in the control group. The significance of the finding was sustained after adjusting for several possible confounding variables.

A recent observational study of depressed patients first reported the association between depression and CFH (Zhang *et al.*, 2016). In this study, CFH plasma levels were lower in the depressed group than in the control group, and a specific polymorphism of the CFH gene was associated with depression. This suggested that downregulation of CFH induced the activity of the immune response. This result is interesting, as it contradicts the association between serum CFH and depression in this study. The mean age of the study participants was lower than that of the participants in our study (29 years (SD 5.9) in the depressed group and 31 years (SD 6.8) in the control group). If the age difference of the study participants had an effect on the results regarding the complement system, it may be assumed that the pathway through which the complement system contributes to depression varies with age. Nevertheless, as our finding was opposite to that found by Zhang *et al.*, further investigation is required to verify this assumption.

The effect of CFH on geriatric depression is unclear. However, it is important to note that this study suggested new evidence of high plasma CFH levels in elucidating the relationship between geriatric depression and inflammation.

Possible mechanisms can be suggested to explain the significant increase in CFH in the depressed group compared with the control group in the present study. First, it may concern the regulatory activity of the complement system in increased innate immune activity in the depressed elderly. As described in the *Introduction* section, disruption of the peripheral immune system during aging leads to an excessive innate immune response (Gruver *et al.*, 2007). Studies have indicated

that geriatric depression is closely associated with increased innate immunity. The complement system is a major defender as a participant in innate immunity. The complement system can be activated through three pathways; the classical, lectin, and alternative pathways. The alternative pathway is activated continuously, and active control is needed to prevent cell damage (Muller-Eberhard, 1988; Liszewski *et al.*, 1996). CFH is the key regulator in inhibiting the alternative pathway. In our study, plasma CFH levels were higher in the depressed elderly. This implies that the regulation of the alternative pathway by CFH may be enhanced in depressed elderly. Similar to our finding, a study with patients with relapsed multiple sclerosis (more involvement by innate immunity than acquired immunity) showed elevation of CFH and the authors considered it to indicate chronic activation of the alternative pathway contributing to the disease (Ingram *et al.*, 2010). Another study also reported that the CFH level was increased in patients with multiple sclerosis (Abdel Rasol *et al.*, 2015). There have been several other studies supporting the notion that activity of the alternative pathway contributes to the pathophysiology of inflammation-related diseases, although they did not report elevated CFH levels (Oksjoki *et al.*, 2003; Weiszhar *et al.*, 2013). In age-related macular degeneration, although the systemic CFH level was not significantly increased, the levels of alternative pathway components were increased with the polymorphism of the *CFH* gene (Scholl *et al.*, 2008).

However, we did not confirm increase in innate immunity in the depressed group. Therefore, in order to accurately validate the role of CFH elevation in depression, further refined research is needed, measuring both CFH levels and proinflammatory cytokines and other complement components, to ascertain whether the immune response in the elderly is elevated. In particular, it is necessary to investigate the aspect of innate immunity by examining relevant promising inflammatory markers such as CRP, IL-6, IL-1beta, and TNF-alpha or the active products of the alternative pathway such as C3a and C3b.

Interestingly, C3 was not statistically significantly different between the depressed and control groups. First, this may be because C3 is an intermediate product and not the final mediator of inflammation in the alternative pathway. Second, CFH modulates inflammation, by binding to various host ligands and chemokines (Kopp *et al.*, 2012), as well as the pivotal function of the regulator of the alternative pathway. This may be why elevation of CFH level is associated with depression, independently of C3.

A second explanation for our main result is that it can be inferred that upregulated expression of CFH in geriatric depression interferes with the neuroprotection offered by the complement system. The complement system is known to mediate the inflammatory response and contribute to the destruction of cells, while it is regarded to have neuroprotective activity that eliminates unnecessary inflammatory responses (Yanamadala and Friedlander, 2010). Heese *et al.* (1998) reported that C3 increased nerve growth factor production *in vitro* and contributed to neuronal cell growth and survival. C3 knockout in rats reduced the formation of synapses (Stevens *et al.*, 2007), and deficiency of C3 in adult rats resulted in impaired neurogenesis (Shinjyo *et al.*, 2009). This evidence supports the suggestion that the alternative pathway of the complement system plays a role in enhancing neuroplasticity and reducing inflammation, that is, its neuroprotective action. Therefore, upregulation of CFH in the alternative pathway of the complement system may inhibit the expression of C3 and reduce its neuroprotective activity.

In our study, the elevation of CFH independently increased the risk of geriatric depression even after adjusting for MMSE-KC scores. High blood CFH levels are observed in studies of various neurodegenerative diseases such as AD, multiple sclerosis, and age-related macular degeneration (Hye *et al.*, 2006; Hakobyan *et al.*, 2008; Ingram *et al.*, 2010). It is common for depression to be present in the early stages of neurodegenerative diseases such as dementia (Meyers, 1998), and further studies should be conducted to ascertain whether the CFH elevation observed in this study may lead to decline in cognitive function due to neurodegeneration.

The correlation between GDS scores and plasma level of CFH in depressed patients was not significant. Plasma level of CFH is higher in the depressed group than in the control group, but it did not reflect the severity of depression in the depressed group. Therefore, the plasma level of CFH may reflect the trait of late-life depression, but is not likely to reflect state.

This study has several limitations. First, the diagnosis of depression was achieved through structured interviews using the MINI and confirmed by a clinical panel, but the study was not conducted in a clinical group of patients with major depression. Second, the use of oral steroids or the presence of immune disorders may be confounding variables, but we did not assess for these factors. Third, it is not clear whether CFH is a trait or state marker of geriatric depression. Further research, following a longitudinal design in a clinical setting, is needed to

give meaning as biomarkers by longitudinal design studies.

Conclusion

In this study, we found that serum CFH levels were higher in older adults with depression than in older non-depressed individuals. To our knowledge, this study was the first to investigate the relevance of CFH in geriatric depression. It may be inferred that the function of the complement system is related to depression in the elderly. We expect that the results of this study will be further refined and reproduced in subsequent studies, considering the limitations described above.

Conflict of interest

The authors declare no conflict of interest.

Description of authors' roles

C. Han conceived and designed the study. C. Shin wrote the manuscript as first authors and performed the literature searches. B.-J. Ham conducted the statistical data analysis. Y.-H. Ko and C.-U. Pae contributed to the interpretation of the analysis results. M. H. Park, D. C. Steffens, and A. A. Patkar reviewed and revised the manuscript critically. All authors contributed significantly to the study, and have approved the final manuscript.

Acknowledgments

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HC15C1405).

References

Abdel Rasol, H. A., Helmy, H. and Aziz, M. A. (2015). Serum complement factor H and Tyr402 his gene polymorphism among Egyptians with multiple sclerosis. *Neurological Research*, 37, 845–852.

Bae, J. N. and Cho, M. J. (2004). Development of the Korean version of the Geriatric Depression Scale and its short form among elderly psychiatric patients. *Journal of Psychosomatic Research*, 57, 297–305.

Bremmer, M. A. *et al.* (2008). Inflammatory markers in late-life depression: results from a population-based study. *Journal of Affective Disorders*, 106, 249–255.

Bruunsgaard, H., Pedersen, M. and Pedersen, B. K. (2001). Aging and proinflammatory cytokines. *Current Opinion on Hematology*, 8, 131–136.

Cohen, J. (1992). A power primer. *Psychological Bulletin*, 112, 155–159.

de Cordoba, S. R., Tortajada, A., Harris, C. L. and Morgan, B. P. (2012). Complement dysregulation and disease: from genes and proteins to diagnostics and drugs. *Immunobiology*, 217, 1034–1046.

Dilger, R. N. and Johnson, R. W. (2008). Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. *Journal of Leukocyte Biology*, 84, 932–939.

Gasque, P., Dean, Y. D., McGreal, E. P., VanBeek, J. and Morgan, B. P. (2000). Complement components of the innate immune system in health and disease in the CNS. *Immunopharmacology*, 49, 171–186.

Gruver, A. L., Hudson, L. L. and Sempowski, G. D. (2007). Immunosenescence of ageing. *Journal of Pathology*, 211, 144–156.

Hakobyan, S. *et al.* (2008). Measurement of factor H variants in plasma using variant-specific monoclonal antibodies: application to assessing risk of age-related macular degeneration. *Investigative Ophthalmology & Visual Science*, 49, 1983–1990.

Hamilton, G. *et al.* (2007). Complement factor H Y402H polymorphism is not associated with late-onset Alzheimer's disease. *Neuromolecular Medicine*, 9, 331–334.

Han, C., Jo, S. A., Kim, N. H., Jo, I. and Park, M. H. (2009). Study design and methods of the Ansan Geriatric Study (AGE study). *BMC Neurology*, 9, 10.

Heese, K., Hock, C. and Otten, U. (1998). Inflammatory signals induce neurotrophin expression in human microglial cells. *Journal of Neurochemistry*, 70, 699–707.

Hye, A. *et al.* (2006). Proteome-based plasma biomarkers for Alzheimer's disease. *Brain*, 129, 3042–3050.

Ingram, G. *et al.* (2010). Complement regulator factor H as a serum biomarker of multiple sclerosis disease state. *Brain*, 133, 1602–1611.

Jung, I. K., Kwak, D. I., Shin, D. K., Lee, M. S., Lee, H. S. and Kim, J. Y. (1997). A reliability and validity study of geriatric depression scale. *Journal of Korean Neuropsychiatric Association*, 36, 103–112.

Kim, J., Park, M. H., Kim, E., Han, C., Jo, S. A. and Jo, I. (2007). Plasma homocysteine is associated with the risk of mild cognitive impairment in an elderly Korean population. *Journal of Nutrition*, 137, 2093–2097.

Kopp, A., Hebecker, M., Svobodova, E. and Jozsi, M. (2012). Factor H: a complement regulator in health and disease, and a mediator of cellular interactions. *Biomolecules*, 2, 46–75.

Lee, J. H. *et al.* (2002). Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): clinical and neuropsychological assessment batteries. *Journals of Gerontology B: Psychological Sciences and Social Sciences*, 57, P47–53.

Liszewski, M. K., Farries, T. C., Lublin, D. M., Rooney, I. A. and Atkinson, J. P. (1996). Control of the complement system. *Advances in Immunology*, 61, 201–283.

Meyers, B. S. (1998). Depression and dementia: comorbidities, identification, and treatment. *Journal of Geriatric Psychiatry and Neurology*, 11, 201–205.

Muller-Eberhard, H. J. (1988). Molecular organization and function of the complement system. *Annual Review of Biochemistry*, 57, 321–347.

Oksjoki, R., Jarva, H., Kovanen, P. T., Laine, P., Meri, S. and Pentikainen, M. O. (2003). Association between complement factor H and proteoglycans in early human coronary atherosclerotic lesions: implications for local regulation of complement activation. *Arteriosclerosis Thrombosis and Vascular Biology*, 23, 630–636.

Rodriguez de Cordoba, S., Esparza-Gordillo, J., Goicoechea de Jorge, E., Lopez-Trascasa, M. and Sanchez-Corral, P. (2004). The human complement factor H: functional roles, genetic variations and disease associations. *Molecular Immunology*, 41, 355–367.

Scholl, H. P. *et al.* (2008). Systemic complement activation in age-related macular degeneration. *PLoS One*, 3, e2593.

Shinjyo, N., Stahlberg, A., Dragunow, M., Pekny, M. and Pekna, M. (2009). Complement-derived anaphylatoxin C3a regulates in vitro differentiation and migration of neural progenitor cells. *Stem Cells*, 27, 2824–2832.

Stevens, B. *et al.* (2007). The classical complement cascade mediates CNS synapse elimination. *Cell*, 131, 1164–1178.

Thomas, A. J., Davis, S., Morris, C., Jackson, E., Harrison, R. and O'Brien, J. T. (2005). Increase in interleukin-1beta in late-life depression. *American Journal of Psychiatry*, 162, 175–177.

Weiszhar, Z. *et al.* (2013). Elevated complement factor H levels in asthmatic sputa. *Journal of Clinical Immunology*, 33, 496–505.

Yanamadala, V. and Friedlander, R. M. (2010). Complement in neuroprotection and neurodegeneration. *Trends in Molecular Medicine*, 16, 69–76.

Yoo, S.-W. *et al.* (2006). Validity of Korean version of the Mini-International Neuropsychiatric Interview. *Anxiety and Mood*, 2, 50–55.

Zhang, C. *et al.* (2016). Complement factor H and susceptibility to major depressive disorder in Han Chinese. *British Journal of Psychiatry*, 208, 446–452.

Zipfel, P. F., Jokiranta, T. S., Hellwage, J., Koistinen, V. and Meri, S. (1999). The factor H protein family. *Immunopharmacology*, 42, 53–60.