Neurology Asia 2016; 21(4) : 349 – 356

Relationship between serum high-sensitivity C-reactive protein levels and cognitive function in patients with Parkinson's disease

[1,3]Seong-Min Choi *MD PhD*, [1,3]Byeong C. Kim *MD PhD*, [1]Kyung Wook Kang *MD*, [2]Kang-Ho Choi *MD PhD*, [2]Tai-Seung Nam *MD PhD*, [1]Joon-Tae Kim *MD PhD*, [1]Seung-Han Lee *MD PhD*, [1]Man-Seok Park *MD PhD*, [1]Myeong-Kyu Kim *MD PhD*, [1]Ki-Hyun Cho *MD PhD*

[1]Department of Neurology, Chonnam National University Hospital, Gwangju; [2]Department of Neurology, Chonnam National University Hwasun Hospital, Hwasun; [3]National Research Center for Dementia, Gwangju, Korea

Abstract

Inflammation might be associated with cognitive impairment and be involved in the pathogenesis of Parkinson's disease (PD). High-sensitivity C-reactive protein (hs-CRP) is a sensitive biomarker of systemic inflammation. This study aimed to investigate whether serum concentrations of hs-CRP are related to cognitive function in patients with PD. Patients with PD (n = 113, Hoehn and Yahr [H-Y] stage 1-4) underwent evaluation of serum hs-CRP and comprehensive neuropsychological tests that covered the cognitive domains of attention, language, visuospatial function, memory, and executive functions. We categorized subjects with PD as having normal cognition (n=48), mild cognitive impairment (MCI) (n=41), or dementia (n=24). Patients with dementia had a higher hs-CRP level than patients with MCI or normal cognition (2.76 ± 2.53 vs. 1.27 ± 1.99 vs. 0.73 ± 0.88 mg/L, P=0.001). Serum hs-CRP levels were inversely associated with the Mini-Mental State Examination scores and performance on neuropsychological tests of language, visuospatial function, visual memory, and executive function. After controlling for age, sex, symptom duration, education, H-Y stage, and Unified Parkinson's Disease Rating Scale motor score, multiple regression analyses indicated statistically significant associations between hs-CRP levels and performance on neuropsychological tests of visuospatial function, visual memory, and executive function. This study suggests a possible relationship between serum hs-CRP levels and cognitive function in patients with PD, with higher levels of hs-CRP being associated with poor performance on tests of visuospatial function, visual memory, and executive function.

INTRODUCTION

Cognitive impairment is commonly associated with Parkinson's disease (PD), and the prevalence of dementia in PD varies depending on age, disease duration, and the population surveyed.[1] The specific cause and mechanism underlying the development of dementia in patients with PD remain unknown. Inflammation has been suggested to play an important role in the pathogenesis of PD as well as in that of Alzheimer's disease (AD) and the cognitive impairment in general population.[2-4]

C-reactive protein (CRP) is synthesized in the liver and high-sensitivity CRP (hs-CRP) is a sensitive biomarker of systemic inflammation.[5] It is associated with PD as well as cognitive decline, dementia, atherosclerosis, and cardiovascular diseases.[4,6-9] Increased serum hs-CRP levels have been associated with poor cognitive function in the general population[10,11], and an increased risk of AD and vascular dementia.[12-14] However, no association was found between hs-CRP and cognition in other studies involving older persons.[15,16]

Because inflammation appears to play a role in cognitive impairment and PD, we hypothesized the existence of an association between serum hs-CRP levels and cognitive function in patients with PD. This study aimed to compare the level of hs-CRP among PD patients with normal cognition, mild cognitive impairment (MCI), and dementia and to investigate the association between serum concentrations of hs-CRP and cognitive function in these patients.

Address for correspondence: Byeong C. Kim, M.D., Department of Neurology, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju, 501-757, South Korea. Tel: +82-62-220-6123, E-mail: byeong.kim7@gmail.com

METHODS

Subjects

This study involved 113 patients with PD (Hoehn and Yahr [H-Y] stage 1-4). The clinical diagnosis of PD was based on the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD.[17] Exclusion criteria included less than 3 years of education; a history of cerebro-vascular accident, major head injury, other neurologic and psychiatric disorders with significant associated cognitive dysfunction; recent (≤ 3 months) infection or surgery; malignancy or clinically significant systemic disease; current medication with antibiotics, corticosteroids, cholinesterase inhibitor, anticholinergics, memantine, antipsychotics or anxiolytics; and delirium at the time of examination.

All participants gave their informed consent to participate. The study was approved by the Institutional Review Board of the hospital. All participants underwent thorough clinical investigation, including medical history, and physical and neurological examinations by a neurologist. The severity and stage of patients' parkinsonism was assessed during ON-state using the modified H-Y stage[18] and the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore.[19]

We also assessed the presence of hypertension, diabetes mellitus (DM), hyperlipidemia, and cigarette smoking as risk factors affecting the level of hs-CRP and cognition by evaluating the patients' medical history and laboratory findings. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or current use of antihypertensive medications. DM was defined as a fasting glucose level of ≥ 126 mg/dL, random glucose level of ≥ 200 mg/dL, or current use of hypoglycemic agents. Hyperlipidemia was defined as a total cholesterol level of ≥ 240 mg/dL, low-density lipoprotein cholesterol level of ≥ 120 mg/dL, or current use of lipid-lowering agents. Cigarette smoking was defined as present if the patient reported cigarette smoking at least once during the previous 5 years.

Assessment of cognitive function

All patients underwent comprehensive neuropsychological tests[20], which included tests for the following functions: (1) attention: forward and backward digit span and letter cancellation test, (2) language and related functions: reading, writing, comprehension, repetition, and confrontational naming using the Korean version of the Boston Naming Test (BNT)[21], finger naming, right-left orientation, body part identification, calculation, and ideomotor and buccofacial praxis, (3) visuospatial function test: interlocking pentagon drawing and the Rey Complex Figure Test (RCFT), (4) verbal memory test: three-word registration and recall and Seoul Verbal Learning Test (SVLT), (5) visual memory test: the RCFT, immediate recall, 20-min delayed recall, and recognition, and (6) frontal executive function test: motor impersistence, contrasting program, go/no-go, fist-edge-palm test, alternating hand movement, alternating square and triangle, Luria loop, semantic (animal and supermarket) and phonemic Controlled Oral Word Association Test (COWAT), and Stroop test (word and color reading of 112 items). General cognition was measured with the Korean version of mini-mental state examination (MMSE).[22] The neuropsychological tests were performed by a neuropsychologist during the ON-state.

Based on their cognitive profile, all participants were categorized into 3 subgroups: PD-NC (normal cognition), PD-MCI (mild cognitive impairment), and PDD (PD with dementia). PDD was diagnosed according to the Movement Disorder Society (MDS) task force recommendation criteria based on neuropsychological tests and a clinical interview.[23] For all patients with PDD, PD onset preceded the development of dementia by at least 12 months. Using a modified version of the criteria for MCI, subjects without dementia, but who had an observed age- and education corrected z-score deviating more than -1.5 standard deviations (SD) from the expected z-score in at least one cognitive domain, were classified as having PD-MCI.[24] We used a -1.5 SD threshold to minimize the inclusion of cognitively intact patients.

Biochemical analysis

Venous blood samples were drawn for measurements of hs-CRP. The blood samples were centrifuged, and the serum was removed and stored at -70°C until the assay. Serum hs-CRP levels were measured using an immunoturbidimetric analysis (Tina-quant hs-CRP latex assay, Roche/Hitachi, Cobas, Mannheim, Germany) in the Clinical Laboratory of Chonnam National University Hospital. Laboratory personnel were unaware of the clinical details and subject information.

Statistical analysis

The statistical software SPSS version 18.0 for

Windows was used for all statistical analyses. The χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables were used to analyze the demographic and clinical variables among the three groups. Pearson's correlation and stepwise multiple regression analyses were performed to assess the association between serum hs-CRP levels and cognitive function test scores in all PD groups. The results were considered statistically significant at a p-value ≤ 0.05.

RESULTS

Demographic and clinical characteristics of the 113 patients with PD are presented in Table 1. Participants had an average age of 69.1 years (SD = 7.4), 30.8-month duration of symptoms (SD = 34.0), 8.9 years of education (SD = 4.1), and obtained an average MMSE score of 25.1 (SD = 3.8). The mean H-Y stage was 2.0 (SD = 0.8) and the mean UPDRS motor score was 22.4 (SD = 10.5). Forty-eight subjects were classified as PD-NC, 41 as PD-MCI, and 24 as PDD. There were no differences in sex ratio, education level, and prevalence of hypertension, DM, hyperlipidemia, and smoking among the three groups. There were significant differences in age, symptom duration, H-Y stage, UPDRS motor score, MMSE score, and hs-CRP levels among the groups. The PDD group had a higher hs-CRP level than the PD-MCI or the PD-NC groups. However, there was no significant difference in the hs-CRP level between the PD-MCI group and the PD-NC group (Table 1, 2).

Before correlation analyses between the hs-CRP levels and cognitive performance, we tested the potential relationship between hs-CRPs and specific demographic variables that could confound performance on outcome measures. There were significant associations between some demographic variables (symptom duration and H-Y stage) and hs-CRP levels. There were no significant associations between other demographic variables (age, UPDRS motor score, and education) and hs-CRP levels. In addition, there was no significant difference in the hs-CRP levels between men and women.

Correlational analyses were then conducted to examine the relationship between hs-CRP levels and cognitive function test scores. Serum hs-CRP levels were inversely associated with MMSE scores and performance on neuropsychological tests of language, visuospatial function, visual memory, and executive function (Table 2).

After controlling for age, sex, symptom duration, education, H-Y stage, and UPDRS motor score, multivariate linear regression analyses indicated statistically significant associations between hs-CRP levels and performance on neuropsychological tests of visuospatial function, visual memory, and executive function.

Table 1: Demographic and clinical characteristics of patients with Parkinson's disease.

	PD-NC (n = 48)	PD-MCI (n = 41)	PDD (n = 24)	p-value
Age, years	67.2 ± 7.8	70.5 ± 6.0	71.9 ± 6.6	0.001
Sex (male/female)	19/29	21/20	11/13	NS
Symptom duration (months)	21.1 ± 17.1	26.9 ± 28.8	75.5 ± 53.9	< 0.001
Hoehn-Yahr stage	1.4 ± 0.6	2.1 ± 0.6	2.9 ± 1.0	< 0.001
UPDRS motor	16.9 ± 8.1	23.3 ± 10.2	30.1 ± 12.8	0.001
Hypertension (%)	20 (41.6)	17 (41.4)	7 (50.0)	NS
Diabetes mellitus (%)	6 (12.5)	12 (29.2)	3 (21.4)	NS
Hyperlipidemia (%)	12 (25.0)	11 (26.8)	4 (28.5)	NS
Smoking (%)	3 (6.5)	7 (17.0)	4 (28.5)	NS
MMSE	27.1 ± 2.1	25.3 ± 2.3	18.1 ± 3.7	< 0.001
Education (years)	9.0 ± 3.9	8.7 ± 4.3	9.1 ± 4.2	NS
hs-CRP (mg/L)	0.73 ± 0.88	1.27 ± 1.99	2.76 ± 2.53	0.001

PD-NC = Parkinson's disease with normal cognition; PD-MCI = Parkinson's disease with mild cognitive impairment; PDD = Parkinson's disease with dementia; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; hs-CRP = high-sensitivity C-reactive protein; NS = non-significant.

Table 2: Correlations between demographic and clinical variables and levels of high-sensitivity C-reactive protein in all patients with Parkinson's disease (n=113)

	hs-CRP	
	γ	p-value
Age, years	0.107	NS
Symptom duration, months	0.324	0.001
Hoehn-Yahr stage	0.324	0.001
UPDRS motor	0.179	NS
Education, years	-0.068	NS

hs-CRP = high-sensitivity C-reactive protein; UPDRS = Unified Parkinson's Disease Rating Scale; NS = non-significant.

Performance on RCFT, delayed recall and recognition of RCFT, and Stroop word reading tests negatively correlated with hs-CRPs levels. No significant associations were found in the multivariate regression analyses between hs-CRP levels and MMSE scores and performance on neuropsychological tests of language (Table 3).

Table 3: Correlations between levels of high-sensitivity C-reactive protein and cognitive function test outcomes in all patients with Parkinson's disease. (n = 113)

	hs-CRP	
	γ	p-value
MMSE	-0.439	< 0.001
Attention		
Digit span forward	-0.199	0.054
Digit span backward	-0.156	0.133
Language		
BNT	-0.337	0.001
Visuospatial function		
RCFT copy	-0.480	< 0.001
Memory		
SVLT delayed recall	-0.156	0.132
SVLT recognition	-0.196	0.058
RCFT delayed recall	-0.403	0.001
RCFT recognition	-0.302	0.003
Executive function		
COWAT semantic	-0.268	0.011
COWAT phonemic	-0.315	0.003
Stroop word reading	-0.379	< 0.001
StrWR reaction time	0.336	0.002
Stroop color reading	-0.272	0.009
StrCR reaction time	0.145	0.109

hs-CRP = high-sensitivity C-reactive protein; MMSE = Mini-Mental State Examination; BNT = Boston Naming Test; RCFT = Rey Complex Figure Test; SVLT = Seoul Verbal Learning Test; COWAT = Controlled Oral Word Association Test; StrWR = Stroop word reading; StrCR = Stroop color reading.

Table 4: Multiple regression analyses predicting cognitive test scores with high-sensitivity C-reactive protein levels in all patients with Parkinson's disease. (n = 113)

	hs-CRP		
	β	p-value	95% CI
MMSE	-0.137	0.184	-0.827; 0.162
Attention			
Digit span forward	-0.021	0.845	-0.216; 0.177
Digit span backward	-0.087	0.475	-0.173; 0.082
Language			
BNT	-0.190	0.090	-2.905; 0.216
Visuospatial function			
RCFT copy	-0.284	0.013	-3.687; -0.446
Memory			
SVLT delayed recall	0.040	0.724	-0.278; 0.398
SVLT recognition	-0.175	0.137	-0.720; 0.101
RCFT delayed recall	-0.192	0.015	-3.487; -0.398
RCFT recognition	-0.311	0.013	-1.517; -0.185
Executive function			
COWAT semantic	-0.054	0.629	-1.348; 0.821
COWAT phonemic	-0.125	0.268	-1.978; 0.559
Stroop word reading	-0.338	0.004	-5.986; -1.160
StrWR reaction time	0.227	0.022	0.869; 10.963
Stroop color reading	-0.144	0.190	-6.572; 1.330
StrCR reaction time	0.110	0.393	-0.921; 2.309

hs-CRP = high-sensitivity C-reactive protein; 95% CI = 95% Confidence Interval; MMSE = Mini-Mental State Examination; BNT = Boston Naming Test; RCFT = Rey Complex Figure Test; SVLT = Seoul Verbal Learning Test; COWAT = Controlled Oral Word Association Test; StrWR = Stroop word reading; StrCR = Stroop color reading.

DISCUSSION

In this cross-sectional study of the relationship between serum hs-CRP levels and cognitive performance in patients with PD, there were significant associations between the hs-CRP levels and visuospatial function, visual memory, and executive function. Higher levels of serum hs-CRP were associated with poor performance on RCFT, delayed recall and recognition of RCFT, and Stroop word reading tests. The magnitude of the findings remained consistent after adjustment for potential confounders. Our results are in line with a previous report that described significant associations between high levels of CRP in the cerebrospinal fluid (CSF) and cognitive impairment in patients with PD.[25] Although we assessed hs-CRP levels not in the CSF but in the serum, it is possible that the peripheral concentrations of inflammatory proteins, such as hs-CRP and fibrinogen, may reflect neuroinflammatory changes in the central nervous system.[26] However, our conclusion should be accepted with caution because data from another study did not support this conclusion.[26] Mean serum hs-CRP value was not significantly different between PD patients without dementia and those with dementia in a previous report[26], though they did not study an association between hs-CRP levels and specific cognitive function domains.

Inflammation has been suggested to play an important role in the pathogenesis of PD, AD, and other types of dementia.[26,27] Furthermore, inflammation has been related to the pathogenesis of cardiovascular disease, obesity, and insulin

resistance, which in turn have been associated with the risk of cognitive impairment.[8,9,28] Basic experiments also support a role for inflammation in the pathogenesis of AD and other neurodegenerative diseases.[27] Therefore, inflammation may account partly for the cognitive deterioration in older people. Higher levels of inflammatory markers were negatively associated with cognitive function.[29] Hs-CRP is a well-studied biomarker of systemic inflammation.[5] High levels of CRP are reportedly associated with cognitive decline in the general population and in people with MCI and AD.[6,7] Our results are in line with reports that describe an association between elevated CRP levels and poor cognitive performance.[6,7,11,12] However, other studies have questioned the nature of this relationship in an aged (>75 years) group.[30,31] The relationship between peripheral markers of inflammation and cognitive decline seems to be complex and influenced by a number of factors.

In this context, plasma levels of CRP might be confounded with motor disability. Plasma levels of CRP might be associated with motor disturbances in advanced PD, because respiratory infections are common complications due to motor deteriorations.[32] Several studies have suggested that plasma levels of CRP are elevated in PD and are associated with motor and non-motor symptoms.[4,33,34] Significant associations of hallucinations/illusions with plasma CRP levels suggest that high levels of CRP may be associated with the development of dementia in patients with PD.[33] The association between hs-CRP and H-Y stage in our study suggested the possible confounding relationship between the motor disturbances and serum levels of CRP. However, after adjustment of the clinical variables, which affect the hs-CRP levels, serum hs-CRP levels were significantly related to visuospatial function, visual memory, and executive function. These data suggest that the elevation of serum hs-CRP levels is associated with cognitive dysfunction in patients with PD and this association is independent of motor disability, symptom duration, or cardiovascular risk factors.

Several potential mechanisms might explain an association between hs-CRP and cognitive function in patients with PD. Inflammation may be associated with cognitive dysfunction through vascular mechanisms. Inflammation is associated with cardiovascular and cerebrovascular disease, and both diseases could contribute to dementia.[35] Poor cognitive functions, particularly executive function and processing speed, are related to cardiovascular risk factors, inflammation, and brain structural abnormalities.[36,37] The association of hs-CRP and executive function in our study might support this hypothesis. It is also possible that inflammation is associated with cognitive dysfunction through cytokines. Cytokines play a role in numerous healthy-state cognitive processes at the molecular level through pathways such as synaptic plasticity, neurogenesis, and neuromodulation.[35,38] Cytokines mediate cellular mechanisms involved in cognition such as cholinergic and dopaminergic pathways and can facilitate neurodegeneration or regeneration.[38] It is noteworthy that recent works by several investigators have implicated a possible role for gastrointestinal and other infections in the inflammatory hypothesis of PD pathogenesis.[39-42]

The present study has several limitations. First, there could be possible errors in the clinical diagnosis of some patients, because we used clinical criteria for establishing the diagnosis of PD and did not obtain any pathological confirmation. Second, we used many exclusion criteria to minimize the factors influencing the cognition and hs-CRP levels. However, those exclusion criteria can cause selection bias. Third, we did not consider other risk factors for cognitive dysfunction, such as apolipoprotein E and family history of dementia. Fourth, numerous triggers can result in elevated hs-CRP levels; we could not exclude the influence of other conditions that increase inflammation, although the results remained significant even after accounting for several cardiovascular risk factors. Fifth, this was a cross-sectional study; thus, the associations observed here cannot be considered as definitive evidence of a causal relationship.

In conclusion, the present results suggest a possible relationship between serum hs-CRP levels and cognitive function in patients with PD. Higher levels of hs-CRP were associated with poor performance on tests of visuospatial function, visual memory, and executive function. The possible association of hs-CRP levels with cognitive function is important, because management of inflammation is likely to have beneficial effects on the cognition of patients with PD. Future studies are needed to determine whether high hs-CRP levels are a causal factor in the development of cognitive dysfunction or dementia in PD.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Brain Research Program through the National

Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning NRF-2014M3C7A1046041 (to BC Kim).

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. *Neurology* 2009; 72(Suppl 4):S1-S136.
2. McGeer PL, McGeer EG. Inflammation, autotoxicity and Alzheimer disease. *Neurobiol Aging* 2001; 22:799-809.
3. Akiyama H, Barger S, Barnum S, *et al*. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000; 21:383-421.
4. Song IU, Kim JS, Chung SW, Lee KS. Is there an association between the level of high-sensitivity C-reactive protein and idiopathic Parkinson's disease? A comparison of Parkinson's disease patients, disease controls and healthy individuals. *Eur Neurol* 2009; 62:99-104.
5. Pearson TA, Mensah GA, Alexander RW, *et al*. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107:499-511.
6. Xu G, Zhou Z, Zhu W, Fan X, Liu X. Plasma C-reactive protein is related to cognitive deterioration and dementia in patients with mild cognitive impairment. *J Neurol Sci* 2009; 284:77-80.
7. Marioni RE, Stewart MC, Murray GD, *et al*. Peripheral levels of fibrinogen, C-reactive protein, and plasma viscosity predict future cognitive decline in individuals without dementia. *Psychosom Med* 2009; 71:901-6.
8. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342:836-43.
9. Hak AE, Stehouwer CD, Bots ML, *et al*. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol* 1999; 19:1986-91.
10. Teunissen CE, van Boxtel MP, Bosma H, *et al*. Inflammation markers in relation to cognition in a healthy aging population. *J Neuroimmunol* 2003; 134:142-50.
11. Yaffe K, Lindquist K, Penninx BW, *et al*. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003; 61:76-80.
12. Engelhart MJ, Geerlings MI, Meijer J, *et al*. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* 2004; 61:668-72.
13. Schmidt R, Schmidt H, CurbJD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol* 2002; 52:168-74.
14. Ravaglia G, Forti P, Maioli F, *et al*. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. *Neurobiol Aging* 2007; 28:1810-20.
15. Weuve J, Ridker PM, Cook NR, Buring JE, Grodstein F. High-sensitivity C-reatvie protein and cognitive function in older women. *Epidemiology* 2006; 17:183-9.
16. Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. *Neurology* 2005; 64:1371-7.
17. Gibb WR, Lees AJ. The relevance of Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988; 51:745-52.
18. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17:427-42.
19. Fahn S, Elton R, Marsden C. Unified Parkinson's disease rating scale. In: Fahn S, Marsden C, Goldstein M, Calne D. (Eds.), Recent Developments in Parkinson's Disease. McMillan Healthcare Information, Florham Park, NJ, 1987, pp. 153-163.
20. Kang Y, Na DL. Seoul Neuropsychological Screening Battery. Incheon: Human Brain Research & Consulting Co; 2003.
21. Kim H, Na DL. Normative data on the Korean version of the Boston Naming Test. *J Clin Exp Neuropsychol* 1999; 21:127-33.
22. Kang Y, Na DL, Hahn S. A validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. *J Korean Neurol Assoc* 1997; 15:300-8.
23. Dubois B, Burn D, Goetz C, *et al*. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord* 2007; 22:2314-24.
24. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; 256:183-94.
25. Lindqvist D, Hall S, Surova Y, *et al*. Cerebrospinal fluid inflammatory markers in Parkinson's disease – Associations with depression, fatigue, and cognitive impairment. *Brain Behav Immun* 2013; 33:183-9.
26. Song IU, Kim YD, Cho HJ, Chung SW. Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? *Intern Med* 2013; 52:1787-92.
27. Yang J, Fan C, Pan L, *et al*. C-reactive protein plays a marginal role in cognitive decline: a systematic review and meta-analysis. *Int J Geriat Psychiatry* 2015; 30:156-65.
28. Kivipelto M, Ngandu T, Fratiglioni L, *et al*. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005; 62:1556-60.
29. Teunissen CE, Lütjohann D, von Bergmann K, *et al*. Combination of serum markers related to several mechanisms in Alzheimer's disease. *Neurobiol Aging* 2003; 24:893-902.
30. Silverman JM, Beeri MS, Schmeidler J, *et al*. C-reactive protein and memory function suggest antagonistic pleiotropy in very old nondemented subjects. *Age Ageing* 2009; 38:237-14.

31. Lima TS, Adler AL, Minett T, Matthews FE, Brayne C, Marioni RE; Medical Research Council Cognitive Function and Ageing Study. C-reactive protein, APOE genotype and longitudinal cognitive change in an older population. *Age Ageing* 2014; 43:289-92.
32. Fernandez HH, Lapane KL. Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. *Med Sci Monit* 2002; 8:241-6.
33. Sawada H, Oeda T, Umemura A, *et al*. Subclinical elevation of plasma C-reactive protein and illusions/ hallucinations in subjects with Parkinson's disease: case-control study. *PLoS One* 2014; 9:e85886.
34. Zhang L, Yan J, Xu Y, *et al*. The combination of homocysteine and C-reactive protein predicts the outcomes of Chinese patients with Parkinson's disease and vascular parkinsonism. *PLoS One* 2011; 6:e19333.
35. Wichmann MA, Cruickshanks KJ, Carlsson CM, *et al*. Long-term systemic inflammation and cognitive impairment in a population-based cohort. *J Am Geriatr Soc* 2014; 62:1683-91.
36. Knopman D, Boland LL, Mosley T, *et al*. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 2001; 56:42-8.
37. Windham BG, Simpson BN, Lirette S, *et al*. Associations between inflammation and cognitive function in African Americans and European Americans. *J Am Geriatr Soc* 2014; 62:2303-10.
38. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* 2009; 33:355-66.
39. Fasano A, Bove F, Gabrielli M, *et al*. The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* 2013; 28:1241-9.
40. Tan AH, Mahadeva S, Thalha AM, *et al*. Small intestinal bacterial overgrowth in Parkinson's disease. *Parkinsonism Relat Disord* 2014; 20:535-40.
41. Tan AH, Mahadeva S, Marras C, *et al*. Helicobacter pylori infection is associated with worse severity of Parkinson's disease. *Parkinsonism Relat Disord* 2015; 21:221-5.
42. Bu XL, Wang X, Xiang Y, *et al*. The association between infectious burden and Parkinson's disease: A case-control study. *Parkinsonism Relat Disord* 2015; 21:877-81.