Is Neuroinflammation Involved in the Development of Dementia in Patients with Parkinson’s Disease?

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Objective

High-sensitivity C-reactive protein (hs-CRP) is an extremely sensitive systemic marker of inflammation and tissue damage, and increased levels of hs-CRP are strongly associated with inflammatory reactions. Microglia-mediated neuroinflammation has been hypothesized to play an important role in the pathogenesis of idiopathic Parkinson’s disease (PD). However, the clinical value of the hs-CRP level in patients with PD is poorly defined. Therefore, we conducted this study to analyze the differences in the hs-CRP levels in PD patients with and without dementia.

Methods

We examined 72 PD patients without dementia (PDwoD) and 45 PD patients with dementia (PDD), as well as 84 control subjects. We investigated the differences in the hs-CRP and fibrinogen levels between these three groups.

Results

The mean hs-CRP and fibrinogen values were not significantly different between the PDwoD and PDD groups; however, these two groups had significantly higher mean hs-CRP and fibrinogen values than the control group.

Conclusion

It is known that inflammation plays a role in the pathogenesis of PD and dementia. However, based on the results of this study, we cautiously speculate that although neuroinflammation plays a role in the development of neurodegenerative diseases, including PD and dementia, it may be unrelated to the pathogenesis of dementia in patients with PD.

Key words: neuroinflammation, high-sensitivity C-reactive protein, fibrinogen, Parkinson’s disease, dementia

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in patients with AD. Because inflammation appears to play a role in the pathogenesis of AD, it has been suggested that NSAID therapy may influence both the onset and progression of AD (1, 4, 8). However, few studies have so far examined the effects of inflammation on dementia in patients with PD.

Inflammation is also known to play an important role in the pathogenesis of atherosclerosis, and various markers of inflammation have been investigated as potential predictors of cardiovascular and cerebrovascular disease (9, 10). Of these markers, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen are well-studied biomarkers of systemic inflammation (11). Accordingly, these two biomarkers have attracted clinical attention as potential predictive markers of atherosclerosis. Furthermore, many previous reports have suggested that high concentrations of hs-CRP and fibrinogen are associated with an increased risk of cardiovascular disease, stroke and cognitive impairment, including dementia (1, 6, 10, 12, 13). Therefore, in this study, we compared the levels of hs-CRP and fibrinogen, the most studied biomarkers of systemic inflammation, between PD patients with dementia (PDD) and PD patients without dementia (PDwoD), as well as normal control group subjects, to clearly evaluate the effects of inflammation on the occurrence of dementia in PD patients.

Materials and Methods

This study was approved by the local ethics committee of our institution, and all patients provided their written informed consent prior to participation. A series of consecutive patients were admitted to the Movement Disorder and Parkinson’s Disease Unit of the Department of Neurology at the Catholic Medical Center of Korea between October 2010 and December 2011. Data for 117 PD patients (72 PDwoD and 45 PDD) recruited for this study were compared with those of 84 controls. There were no significant differences in age or sex between the healthy controls and the PD patients.

To compare only the PDwoD and PDD subjects, patients with a clinical dementia rate (CDR) score of ≥0.5 and a mini-mental status examination (MMSE) score of ≥24 points were included in this study. The subjects in the control group did not have any history or symptoms of PD, memory impairment or other types of cognitive impairment, according to the results of a dementia screening questionnaire. Additionally, the control subjects did not have a history of other neurological diseases, such as head trauma, epilepsy, cerebrovascular disease or brain surgery. All of the subjects were examined at both the dementia clinic and the movement disorder clinic of Incheon St. Mary’s Hospital. The evaluation procedure consisted of taking a detailed medical history, performing physical and neurological examinations, neuropsychological assessments and laboratory tests and obtaining brain magnetic resonance imaging (MRI) and 123I-n-fluoropropyl-2-b-carbomethoxy-3b-(4-iodophenyl) nor-tropane (FP-CIT) positron emission tomography (PET) scans. Information regarding the patient’s history of medical and neurological problems was obtained from the patient, family members and/or other caregivers. All PDD and PDwoD patients were diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank Clinical Diagnosis Criteria for Parkinson’s Disease and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) criteria for dementia (14, 15).

PD patients exhibiting a reduction in their striatal dopamine transporter uptake level were also considered eligible for this study. For all PDD patients, the onset of Parkinson’s disease preceded the development of dementia by at least 12 months. We excluded patients who displayed markedly fluctuating cognition with pronounced variations in attention and alertness, recurrent vivid hallucinations (as suggested by the presence of diffuse Lewy body disease) or any signs of atypical Parkinsonism and those who were taking medications (e.g., anticholinergic agents) that have been reported to influence cognition and memory or patients who fulfilled the DSM-IV-TR criteria for delirium or amnestic disorders (15, 16). The PD patients did not have any history or symptoms of memory impairment or other cognitive dysfunction, according to the dementia screening questionnaire, and had no cerebrovascular lesions on neuroimaging. In addition to the above-mentioned exclusion criteria, we excluded patients with secondary causes of Parkinsonism (e.g., Wilson’s disease, neuroleptic drug use or psychiatric diseases) that could potentially compromise the safety of the study.

None of the subjects included in this study had a history of recent infection as an outpatient or inpatient, surgery or trauma occurring within the previous month, cardiovascular disease, cerebrovascular disease, malignancy or use of NSAIDs, such as ibuprofen or aspirin, as these factors may influence the serum hs-CRP and fibrinogen levels. The control subjects were free of any medical abnormalities, such as infection or neurological deficits.

The severity of motor impairment in the patients with PD was evaluated according to the staging system of Hoehn and Yahr (H & Y stage) (17). The serum hs-CRP and fibrinogen levels were routinely measured in all patients and healthy controls. Venous blood samples were collected from all subjects in tubes containing ethylenediaminetetraacetic acid. The samples were separated using centrifugation at 3,000 rpm for 10 minutes immediately after collection. The separated sera were stored at -70°C until the laboratory evaluation. The laboratory data were collected by an examiner who was blinded to the clinical details and patient information.

We also assessed the presence of hypertension, diabetes mellitus, hypercholesterolemia and cigarette smoking as risk factors affecting the levels of hs-CRP and fibrinogen by evaluating the patients’ medical histories and laboratory findings. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg and a history of antihypertensive medication.
mmHg and/or the current use of antihypertensive medications. Diabetes mellitus (DM) was defined as a history of a fasting glucose level of ≥110 mg/dL or the current use of hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol concentration of ≥220 mg/dL or the current use of lipid-lowering agents. Cigarette smoking was defined as present if the patient reported smoking cigarettes at least once during the past five years.

The statistical analysis was performed using the SPSS software package, version 18.0. The results are expressed as the mean ± standard deviation. The Kruskal-Wallis test was used to compare continuous variables between the two PD groups and the healthy control group. The Mann-Whitney U test was used to compare continuous variables between the two PD groups. Pearson’s Chi-square test was used to compare categorical variables. To evaluate the strength of the associations between the hs-CRP levels, which were categorized as ≤0.5 mg/dL and >0.5 mg/dL, and between the fibrinogen levels, which were categorized as ≤350 mg/dL and >350 mg/dL, we determined the odds ratios using multivariate logistic regression analyses. p values of <0.05 were considered to be statistically significant.

**Results**

The demographic characteristics of all subjects are summarized in Table. There were no overall significant differences in age or gender distribution between the PD patients and the healthy controls. The duration of Parkinsonian symptoms in the PDD and PDwoD groups was not significantly different. Additionally, there were no significant differences between the PDwoD and PDD groups with respect to DM, cigarette smoking, hypercholesterolemia or hypertension. A comparison of the three groups showed that there were no significant differences in the mean hs-CRP or fibrinogen levels between the PDwoD and PDD groups; however, the mean hs-CRP and fibrinogen levels in the two PD groups were significantly higher than those observed in the normal control group (Table; Fig. 1, 2).

According to a logistic regression analysis, the odds ratios of the hs-CRP and fibrinogen levels in the PDD group were 2.017 (95% confidence interval =1.180-3.014) and 1.301 (95% confidence interval =0.168-1.914), respectively, while the odds ratios of the hs-CRP and fibrinogen levels in the PDwoD group were 1.834 (95% confidence interval =1.173-2.802) and 0.571 (95% confidence interval =0.151-1.869), respectively (Fig. 3). The odds ratios of dementia among the PDD and PDwoD patients based on the hs-CRP and fibrinogen levels were 1.453 (95% confidence interval =0.537-3.931, p value =0.462) and 1.789 (95% confidence interval =0.331-9.671, p value=0.500), respectively.

**Discussion**

The pathogenesis of PDD and PD is currently unknown; however, at the cellular level, significant microglial inflammation is observed in regions of dopaminergic degeneration, and some protection against PD is offered by the long-term administration of anti-inflammatory medications (6, 18). In addition, microglia-mediated neuroinflammation has been hypothesized to play an important role in the pathogenesis of PD as well as in the cognitive decline observed in patients with AD (6, 19, 20). The large number of recent reviews on the subject bears witness to the growing realization of the importance of the inflammatory response in the progression of PD, a hypothesis that has received strong sup-

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<td>hs-CRP (mg/dL)**</td>
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PDwoD: Parkinson’s disease without dementia, PDD: Parkinson’s disease with dementia

MMSE: mini-mental status examination
CDR: clinical dementia rate, SOB: sum of box of CDR
hs-CRP: high-sensitivity C-reactive protein,
H & Y stage: Hoehn and Yahr stage, ND: Not done

Values was expressed as mean ± standard deviation
Gender was analyzed by Pearson chi-square test among 3 group
* Values was expressed as number with percentage in parentheses
**p value : PDwoD vs PDD >0.05, PDwoD vs Control<0.05, PDD vs Control<0.05
The involvement of neuroinflammatory responses to microglial activation are observed in the control patients. These findings are consistent with those reported in previous studies; namely, that neuroinflammatory responses to microglial activation are likely to contribute to the degenerative processes observed in PD (5, 9, 21, 24, 29). The involvement of neuroinflammation in the pathogenesis of PD is supported by several reports showing that anti-inflammatory medication use is associated with a reduced risk of PD (6, 30, 31). Furthermore, several studies have suggested that NSAID use may delay or prevent the onset and progression of PD; however, Chen et al. reported that NSAIDs other than ibuprofen have no discernible effects on the risk of PD (1, 4, 30). Consequently, there is conflicting support for the hypothesis that the use of NSAIDs reduces the risk of PD. Nevertheless, several studies have suggested that anti-inflammatory drugs offer a new treatment approach for PD (1, 29). Furthermore, Ouchi et al. showed that the degree of microglial activation is greater in PD patients with more severe damage in the nigrostriatal pathway than in those with less severe damage (29). In their histopathologic study, Orr et al. demonstrated that the pattern of humoral immune reactivity in the brain tissue of PD patients is consistent with the immune activation of microglia leading to the targeting of dopamine nigral neurons for destruction (18). These previous studies therefore suggest that neuroinflammation plays a role in the pathogenesis of PD.

With regard to cognitive impairment, previous studies have also indicated the involvement of inflammatory mechanisms in the pathogenesis of neurodegenerative diseases, such as AD, although the underlying pathological processes that cause tissue destruction in AD patients remain unknown (9, 19, 32). Neuropathological studies have demonstrated the presence of IL-6 and CRP, an acute-phase protein, in plaques obtained from the brains of patients with a decreased cognitive function, such as those with...
AD (4, 8, 32). In contrast, plaques in the brains of non-demented elderly persons did not exhibit IL-6 immunoreactivity (8, 13, 32). However, in this study, we did not find any significant differences in the hs-CRP and fibrinogen levels between the PDwoD and PDD patients. Furthermore, the odds ratios for PDD based on an hs-CRP level cutoff of 0.5 (odds ratio =1.453, 95% confidence interval =0.537-3.931) and a fibrinogen level cutoff of 350 (odds ratio =1.789, 95% confidence interval =0.331-9.671) relative to the PDwoD group were not significant. These results suggest that neither hs-CRP nor fibrinogen play a crucial role in the development of dementia in patients with PD.

A limitation of this study is our use of PDD diagnostic criteria that have not yet been validated. Furthermore, differentiating between PDD and dementia with Lewy bodies on the basis of clinical criteria is difficult, particularly in the early phases of the diseases. In addition, we did not carry out any neuropathological investigations to confirm the presence of Lewy body pathology because the patients were still alive. We attempted to address these confounders by including only patients who fulfilled two sets of diagnostic criteria and exhibited a decreased uptake of dopamine transporters in the basal ganglia on FP-CIT PET, although this selection procedure may have preferentially selected patients with a prior clinical suspicion of PDD.

In conclusion, we found both the hs-CRP and fibrinogen levels to be significantly higher in the PD patients than in the normal controls, which supports the hypothesis that neuroinflammatory reactions are involved in the pathogenesis of PD. However, the levels of hs-CRP and fibrinogen were not associated with the development of dementia in the PD patients; there were no significant differences in the hs-CRP or fibrinogen levels between the PDwoD and PDD groups. Furthermore, the odds ratios for the occurrence of dementia in the PD patients based on the hs-CRP and fibrinogen levels were not significant. Therefore, based on these results, it can be cautiously estimated that neuroinflammation does not influence the pathogenesis of dementia in PD patients. However, our study was not a large-scale longitudinal study, which would be required to clarify whether neuroinflammation plays an important role in the pathogenesis of PDD and provide clearer answers as to whether hs-CRP and fibrinogen are indeed risk factors for the onset of dementia in PD patients.

The authors state that they have no Conflict of Interest (COI).

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