Plasma Pentraxin 3, but not High-sensitivity C-reactive Protein, is a Useful Inflammatory Biomarker for Predicting Cognitive Impairment in Elderly Hypertensive Patients

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Background. Due to the increasing longevity of human populations worldwide, there is need of a useful biomarker for the early detection of cognitive impairment in elderly persons. Both high blood pressure (BP) and inflammatory processes have been reported to be involved in cognitive impairment via cerebrovascular atherosclerosis or neuronal cell damage.

Methods. In this cross-sectional study of 210 ambulatory elderly hypertensive patients without clinically evident dementia (mean age: 74 years; 44% men), we measured 24-hour BP, circulating pentraxin 3 (PTX3) and high-sensitivity C-reactive protein (hs-CRP) levels, and cognitive function (Mini-Mental State Examination [MMSE]).

Results. A high plasma PTX3 level was observed in lean subjects, especially in those whose current body weight was lower than that measured 5 years earlier, whereas a high hs-CRP level was associated with obesity (all \( p < 0.05 \)). Both PTX3 and hs-CRP levels were significantly associated with the MMSE score (\( r = -0.248, p<0.001 \) and \( r = -0.153, p<0.05 \), respectively); however, in multiple regression analysis, the PTX3 level, but not the hs-CRP level, was inversely associated with the MMSE score independently of patient demographics, glucose and lipid metabolic parameters, 24-hour systolic BP (SBP) level, and the atherosclerotic burden (all \( p < 0.05 \)). Moreover, there was a significant interaction between the PTX3 and 24-hour SBP levels in the determinants of MMSE score (\( p < 0.05 \)).

Conclusions. A high plasma PTX3 level in elderly hypertensive patients, particularly in those with a high 24-hour BP level, could be a significant predictor of cognitive impairment. A high PTX3 level may be a marker of frailty in elderly hypertensive patients.

Key Words: Pentraxin 3—High-sensitivity C-reactive protein—Cognitive impairment—Elderly hypertensive patients.

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Along with the increasing longevity of human populations worldwide, the prevention of cognitive impairment in elderly persons has become a major public health challenge, not least because cognitive impairment can cause a cascade of sequelae such as falls, loss of independence, need for hospital care, and even premature cardiovascular- or noncardiovascular-related death (1–3). Thus, it will be important to clarify the pathophysiology of cognitive impairment and establish new and easy-to-use markers for the early identification of those elderly individuals most likely to develop cognitive impairment.

Hypertension is common among elderly persons and is a potent risk factor of cognitive impairment in this population (4). Recent studies have also shown significant associations between chronic inflammation and cognitive impairment in the general population (5–7), and these associations were partly explained by the development of cerebrovascular atherosclerosis or neuronal cell damage stimulated by inflammatory processes themselves (8–10).

C-reactive protein (CRP) is one of the acute-phase inflammatory proteins and is produced primarily by hepatocytes; CRP has been reported to be associated with cognitive impairment cross-sectionally and longitudinally in general populations (5–7). However, CRP is a nonspecific inflammatory marker that increases with obesity (11), and thus the association between CRP levels and cognitive impairment...
in elderly persons is likely to be complex, because some previous studies, but not all, have found leanness or body
weight (BW) loss to be associated with cognitive impairment
in elderly persons (12–16).

Pentraxin 3 (PTX3) belongs to the CRP family but is
synthesized by cells directly involved in atherosclerosis,
including vascular endothelial cells, smooth muscle cells,
among macrophages (17,18); thus, its in vivo level may more
directly reflect the inflammatory status of the vasculature
than the in vivo level of CRP. Moreover, the level of PTX3
increases with leanness (19,20); therefore, a high PTX3
level in elderly persons may represent a weight loss (wast-
ing) condition or frailty (1,2). Accordingly, we hypothesized
that the PTX3 level is a more accurate and effective marker
and predictor of cognitive impairment in elderly persons
than the CRP level.

In the present study, we examined the association
between inflammatory biomarkers (PTX3 and high-sensitivity
[hs]-CRP) and cognitive function (Mini-Mental State
Examination [MMSE]) in elderly hypertensive patients
without clinically evident dementia and attempted to deter-
mine which is the better biomarker of cognitive impairment.
Moreover, we also examined whether there is a significant
interaction between these inflammatory biomarkers and
24-h blood pressure (BP) level as potential determinants
of cognitive impairment.

**Methods**

**Patients**

From May 2008 to December 2008, 216 consecutive
patients with essential hypertension who were 60 years or
older and who had been treated at our outpatient clinic
(Nango National Health Insurance Hospital, Miyazaki,
Japan) were recruited for this study. Hypertension was
defined as office BP greater than or equal to 140/90 mm Hg
or current use of antihypertensive drugs (21). The enrolled
patients were ambulatory elderly persons living indepen-
dently and were not nursing home residents. The exclusion
criteria were as follows: any difficulty with activities of
daily living, clinical dementia based on Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition
criteria or confirmation based on the patient’s medical records,
inability to communicate with the interviewer, a recent his-
tory (within 6 months) of cardiovascular disease (coronary
arterial disease [CAD] and cerebrovascular disease) or heart
failure, presence of inflammatory diseases (acute infection
and autoimmune diseases), presence of malignant disease,
atrial fibrillation (due to the inaccuracy of BP measurement
by automated devices in patients with this condition; 22),
and absence of or incomplete sampling data. All patients
completed a health questionnaire and provided their com-
plete medical history (see Supplementary data). This study
was approved by the institutional review board at Jichi
Medical University, and written informed consent was
obtained from all participants.

**Anthropometric Assessment**

All patients underwent measurement of body mass index
(BMI) and waist circumference at the umbilical portion.

**BP Assessment**

Office BP was measured by a digital oscillometric BP
monitoring device (HEM-5041; Omron Healthcare, Co.,
Ltd, Kyoto, Japan) and calculated as the mean of three
consecutive measures. Ambulatory BP monitoring (ABPM;
TM-2425; A&D Co. Inc., Tokyo, Japan) was performed
with an automatic device at 30-minute intervals during
the daytime and nighttime (23). All subjects used their
prescribed antihypertensive medications as usual during
ABPM.

**Laboratory Testing**

Peripheral venous blood was obtained via a 21-gauge
needle, with the patient in the fasting state, between 08:00
am and 08:30 pm. Plasma was obtained by centrifuging
the whole blood at 1500g for 15 minutes at 4°C, and samples
were immediately frozen and stored at −40°C until used for
analysis. The concentration of hs-CRP (N hs–CRP; Dade
Behring Inc., Liederbach, Germany) was measured by SRL
Inc. (Tokyo, Japan). Plasma PTX3 was measured by a com-
mercially available enzyme-linked immunosorbent assay
kit (Perseus Proteomics Inc., Tokyo, Japan). The intra-assay
and interassay variation coefficients of each test were
both less than 7%. All measurements were performed within
6 months.

**Assessment of Cognitive Function**

Cognitive function was assessed using the MMSE score.
The methods used for this examination have been described in
detail elsewhere (14). The MMSE values range from 0 to 30.

**Carotid Ultrasonography**

For full details, see Supplementary data. Briefly, the
carotid arteries were examined bilaterally at the level of the
common carotid artery (CCA), the bulb, and the internal
carotid artery, as measured from both transverse and longitudi-
unal orientations. The region with the thickest intima-media
thickness (IMT) was measured and was included in our anal-
ysis, and the value was calculated as the mean of the single
thickest point in the far wall on both sides of the structure.
Statistical Analysis

All statistical analyses were performed using SPSS version 16.0J software (SPSS, Chicago, IL). Data are expressed as the means ± standard deviation or median (interquartile range). The associations between the individual parameters were calculated using Spearman’s correlation method. To assess independent associations between the PTX3 or hs-CRP levels and the MMSE score, we used a stepwise multivariable linear regression analysis. In the initial model (Model 1), the associations of the PTX3 or hs-CRP levels and the MMSE score were assessed with adjustment for age, sex, BMI, ever-smoker status, education level, a previous history of cardiovascular disease, and renal function. Extended models were used to assess whether the influence of both the PTX3 and hs-CRP levels on the MMSE score was attenuated by the potential confounding effects of BP parameters (Model 2), glucose and lipid metabolic parameters (Model 3), and atherosclerotic burden (Model 4). Variables with skewed distribution were logarithmically transformed prior to the analysis. Statistical significance was defined as the p < .05 level in all analyses.

RESULTS

Characteristics of the Study Population

Two patients who refused to participate, one patient with incomplete sample of ABPM and three patients with unsatisfactory blood sampling were excluded. The characteristics of the remaining 210 subjects are given in Table 1. There were five patients with a previous history of CAD and one patient with a previous history of heart failure; however, all these patients were defined as New York Heart Association class I.

Association of PTX3 and hs-CRP Levels With Various Clinical Parameters

The associations between the plasma PTX3 level or serum hs-CRP level and the various clinical parameters are shown in Supplementary Table 1. There was no significant association between the PTX3 and hs-CRP levels themselves (r = −.077; p = .266). The PTX3 level was significantly inversely associated with obesity and hypertriglyceremia, whereas the hs-CRP level was positively associated with obesity and hypertriglyceremia and a low high-density lipoprotein level. Intriguingly, the PTX3 level was inversely associated with the % BW change over the past 5 years (Supplementary Figure 1). The PTX3 level was weakly but significantly associated with the CCA-IMT level, whereas the hs-CRP level was not associated with the CCA-IMT level. None of the medications, including antihypertensive drugs and statins, were associated with either the PTX3 or hs-CRP levels (data not shown).

Association of the MMSE Score and PTX3 and hs-CRP Levels

There were significant associations between the MMSE score and both the PTX3 and hs-CRP levels (Table 2). When the comparisons were restricted to nonobese subjects (BMI < 25 kg/m², n = 119), both the PTX3 and hs-CRP levels remained significantly associated with the MMSE score (r = −.239 and −.260, respectively, both p < .01). In the obese subjects (BMI ≥ 25 kg/m², n = 93), there was a non-significant trend toward an inverse association between the PTX3 level and MMSE score (r = −.197, p = .061), while there was no trend or association between the hs-CRP level and MMSE score (r = −.016, p = .879).

A stepwise multivariate regression analysis showed that the PTX3 level, but not the hs-CRP level, was significantly associated with the MMSE score independently of age, sex, BMI, smoking status, education level, a previous history of cardiovascular disease, and renal function (Model 1; Table 3). The independent association between the MMSE score and the PTX3 level was evident even after adjustment for BP parameters (Model 2; Table 3), glucose and lipid metabolic parameters (Model 3; Table 3), and the extent of atherosclerotic burden (ie, CCA-IMT level, Model 4; Table 3). When the PTX3 and hs-CRP levels were concomitantly entered into the same model (Model 1), the PTX3 level

Table 1. Characteristics of the Study Population (n = 210)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Mean ± SD/SD (25th–75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>210</td>
<td>74.4 ± 6.9</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>210</td>
<td>93 (44)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>210</td>
<td>24.8 ± 3.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>210</td>
<td>84.6 ± 9.0</td>
</tr>
<tr>
<td>Ever-smoker, n (%)</td>
<td>210</td>
<td>76 (36)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>210</td>
<td>8.5 ± 1.5</td>
</tr>
<tr>
<td>Antihypertensive medications, n (%)</td>
<td>210</td>
<td>177 (84)</td>
</tr>
<tr>
<td>Duration of hypertensive medications (years)</td>
<td>210</td>
<td>8.0 (4.0–16.0)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>210</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>210</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>210</td>
<td>19 (9)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>210</td>
<td>67.1 ± 18.7</td>
</tr>
<tr>
<td>Blood pressure measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>210</td>
<td>131.8 ± 12.1</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>210</td>
<td>74.7 ± 6.6</td>
</tr>
<tr>
<td>24-h PR, bpm</td>
<td>210</td>
<td>66.0 ± 7.2</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>210</td>
<td>98.0 (93.0–108.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>210</td>
<td>93.5 (73.5–125.3)</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>210</td>
<td>112.7 ± 27.8</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>210</td>
<td>57.0 (47.0–66.0)</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>210</td>
<td>0.48 (0.23–1.11)</td>
</tr>
<tr>
<td>Pentraxin 3 (ng/mL)</td>
<td>210</td>
<td>2.7 (1.8–3.9)</td>
</tr>
<tr>
<td>Cognitive function (points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>210</td>
<td>25.3 ± 3.0</td>
</tr>
<tr>
<td>Atherosclerotic burden (mm)</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Max CCA-IMT</td>
<td>210</td>
<td>0.92 (0.80–1.08)</td>
</tr>
<tr>
<td>Max ICA-IMT</td>
<td>210</td>
<td>1.18 (0.97–1.49)</td>
</tr>
</tbody>
</table>

Notes: Data are expressed as means ± SD or median (25th–75th). CCA = common carotid artery; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; ICA = internal carotid artery; IMT = intima-media thickness; MMSE = Mini-Mental State Examination; PR = pulse rate; SBP = systolic blood pressure.
Table 2. Spearman’s Correlation Coefficients of MMSE Score and Various Clinical Parameters in Elderly Hypertensive Patients (n = 210)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>−0.324‡</td>
</tr>
<tr>
<td>Sex (0 = men, 1 = women)</td>
<td>0.149*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.142*</td>
</tr>
<tr>
<td>% Body weight change in past 5 years (%)</td>
<td>0.095</td>
</tr>
<tr>
<td>Ever-smoker (0 = no, 1 = yes)</td>
<td>−0.160*</td>
</tr>
<tr>
<td>Education (years)</td>
<td>0.391†</td>
</tr>
<tr>
<td>Duration of hypertensive medications (years)</td>
<td>−0.171†</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (0 = no, 1 = yes)</td>
<td>−0.028</td>
</tr>
<tr>
<td>Statin use (0 = no, 1 = yes)</td>
<td>0.152*</td>
</tr>
<tr>
<td>Cardiovascular disease (0 = no, 1 = yes)</td>
<td>−0.158*</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>0.131</td>
</tr>
<tr>
<td>Blood pressure measurement (mm Hg)</td>
<td>—</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>−0.205†</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>−0.031</td>
</tr>
<tr>
<td>Biochemical markers</td>
<td>—</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>0.024</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.124</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>0.121</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>0.105</td>
</tr>
<tr>
<td>Pentraxin 3 (ng/mL)</td>
<td>−0.248‡</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>−0.153*</td>
</tr>
<tr>
<td>Cognitive function (points)</td>
<td>—</td>
</tr>
<tr>
<td>MMSE</td>
<td>—</td>
</tr>
<tr>
<td>Atherosclerotic burden (mm)</td>
<td>—</td>
</tr>
<tr>
<td>Max CCA-IMT</td>
<td>−0.189†</td>
</tr>
<tr>
<td>Max ICA-IMT</td>
<td>−0.140*</td>
</tr>
</tbody>
</table>

Notes: Statistical significance was defined as *p < .05; †p < .01; ‡p < .001. CCA = common carotid artery; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; ICA = internal carotid artery; IMT = intima-media thickness; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure.

was independently associated with the MMSE score (β = −0.174, p = .006). Moreover, there were significant interactions between the PTX3 level and 24-hour systolic BP (SBP) level in determining the MMSE score even after adjustment for significant covariates in Model 1 (β = −.167, p = .008).

**Discussion**

In this cross-sectional study of ambulatory independent elderly hypertensive patients without clinically evident dementia, a high plasma PTX3 level, but not a high hs-CRP level, was significantly associated with cognitive impairment independently of patient demographics, glucose and lipid metabolic parameters, and the extent of atherosclerotic burden, and this relation was especially pronounced in those with high 24-hour BP levels. The reason why PTX3, rather than hs-CRP, was a significant inflammatory biomarker for predicting cognitive impairment in our elderly hypertensive patients remains unknown, but there are at least two possible explanations.

First, the associations of obesity with PTX3 and hs-CRP were directly opposite, that is, PTX3 increased with lean- ness, especially in those whose current BW was lower than that measured 5 years earlier, whereas hs-CRP increased with obesity. And thus, the association between hs-CRP and cognitive impairment was confounded by obesity. In fact, our data showed that the significant inverse association between hs-CRP and MMSE score in nonobese subjects was not found in obese subjects.

Obesity in middle age appears to increase the risk for late-life cognitive decline and dementia (13,15), but it is uncertain whether obesity in late life remains a risk factor for cognitive impairment. Some previous studies, but not all, have indicated that leanness or BW loss, rather than obesity, is associated with cognitive impairment in elderly persons (12–16). Our previous report in another population (14) also showed that leanness in elderly hypertensive patients was associated with cognitive impairment, especially in the very elderly subjects (≥80 years). In the present study, we also found a significant association between leanness and cognitive impairment. The mechanism underlying the association between leanness and cognitive impairment is not clear, but an examination of the overlapping biological processes associated with leanness or BW loss and cognitive impairment may provide some explanations.

BW loss and cognitive impairment are two of the important clinical manifestations that have been associated with frailty in elderly persons, which in turn has been significantly associated with excess disability and mortality (1,2). There is increasing evidence of significant positive associations

Table 3. Associations Between MMSE and Both PTX3 and Hs-CRP Levels in Elderly Hypertensive Patients (n = 210)

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>Standardized β</th>
<th>β (95% CI)</th>
<th>p Value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentraxin 3*</td>
<td>Model 1</td>
<td>Age, sex, BMI, ever-smoker, education, cardiovascular disease, eGFR</td>
<td>−0.174</td>
<td>−2.106 (−3.594 to −0.618)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>Model 1 + 24-h SBP + duration of hypertensive treatment</td>
<td>−0.149</td>
<td>−1.804 (−3.277 to −0.331)</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>Model 3</td>
<td>Model 1 + glucose*, triglycerides*, high-density lipoprotein*</td>
<td>−0.174</td>
<td>−2.106 (−3.594 to −0.618)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>Model 4</td>
<td>Model 1 + CCA-IMT level*</td>
<td>−0.174</td>
<td>−2.106 (−3.594 to −0.618)</td>
<td>.006</td>
</tr>
<tr>
<td>Hs-CRP*</td>
<td>Model 1</td>
<td>Age, sex, BMI, ever-smoker, education, cardiovascular disease, eGFR</td>
<td>−0.081</td>
<td>—</td>
<td>.198</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>Model 1 + 24-h SBP + duration of hypertensive treatment</td>
<td>−0.081</td>
<td>—</td>
<td>.198</td>
</tr>
<tr>
<td></td>
<td>Model 3</td>
<td>Model 1 + glucose*, triglycerides*, high-density lipoprotein*</td>
<td>−0.081</td>
<td>—</td>
<td>.198</td>
</tr>
<tr>
<td></td>
<td>Model 4</td>
<td>Model 1 + CCA-IMT level*</td>
<td>−0.081</td>
<td>—</td>
<td>.198</td>
</tr>
</tbody>
</table>

Notes: BMI = body mass index; CCA = common carotid artery; CI = confidence interval; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure.

*Variables with skewed distribution were logarithmically transformed before analysis. Statistical significance was defined as *p < .05.
between frailty and inflammatory biomarkers (eg, CRP and interleukin-6), suggesting the existence of chronic, low-grade systemic inflammation in frail elderly persons (1,2). Therefore, inflammation may be an important link between BW loss and cognitive impairment. In fact, our data showed that the significant association between leanness and cognitive impairment was partly explained by high PTX3 levels, although we cannot infer a cause and effect relationship from our cross-sectional study.

A high PTX3 level has been associated with poor prognosis in elderly patients (24) and patients with heart failure (25) or chronic kidney disease (26), both of which are wasting conditions. In the present study, high PTX3 levels were observed in the patients whose current BW was lower than that measured 5 years earlier, suggesting that a high PTX3 level may be a marker of a wasting condition or frailty. In contrast, the blood level of CRP was increased with obesity (11); therefore, it is unlikely that the circulatory CRP level could be a marker of frailty in elderly persons. This is one of the reasons why the PTX3 level is a more valid marker for predicting cognitive impairment than the hs-CRP level in elderly persons.

Second, PTX3 is highly expressed in atherosclerotic lesions and in vascular cells exposed to inflammatory stimuli (17,18), and thus the blood level is increased in patients with arterial inflammation, such as that due to unstable angina and myocardial infarction (20,27). This may indicate that the PTX3 level more directly reflects an unhealthy vasculature condition than the hs-CRP level. Recently, increasing attention has been paid to the contribution of cerebral small-vessel diseases to cognitive impairment (28). The major pathogenesis of cerebral small-vessel diseases is increased age and hypertension (29), but inflammatory processes have also been implicated in the pathogenesis (8–10). We previously reported that a high plasma level of hs-CRP was associated with increased risk of silent cerebral infarcts in elderly hypertensive patients (30). In the present study, we did not perform brain neuroimaging, which would have allowed us to better assess the association between PTX3 and hs-CRP level and cerebrovascular diseases; however, our data showed that the PTX3 level, but not the hs-CRP level, was significantly associated with the extent of carotid atherosclerosis (Table 2), which is generally considered to reflect not only cerebrovascular diseases but also generalized atherosclerotic burden. However, adjustment for carotid IMT levels did not change the significant association between PTX3 and cognitive impairment, which indicated that other mechanisms may also exist.

Our data showed that a significant interaction between the PTX3 and the 24-hour SBP level was a determinant of cognitive impairment. The mechanisms could not be addressed from our data: a chronic inflammatory state could reflect or directly enhance the development of atherosclerosis, and thus, the coexistence of elevated inflammatory markers and hypertension may be a marker of a group with a greater degree of atherosclerotic burden or neurodegeneration in the brain (4,29).

The present study has several limitations. First, no causal relationship can be inferred from our cross-sectional data, and thus a follow-up study will be needed to establish a causal relationship between inflammation and cognitive decline. Second, medication use was potentially confounding, although our results were unchanged even after adjustment for the antihypertensive drugs and statins used by our patients. Third, our blood samples were stored at −40°C until used for analysis; therefore, a slight change in the concentration of PTX3 induced by protein degradation may have occurred, although all measurements were performed within 6 months. Such a possibility, however, would result in an underestimation of the true strength of the association of plasma PTX3 with the cognitive function. Finally, the MMSE score is known to be useful in screening for dementia, and we previously reported that the MMSE score was associated with global brain atrophy (31); however, MMSE is not a very sensitive means of detecting subtle impairments of cognitive function, and thus in the present study we may have underestimated the true association between inflammation and cognitive impairment.

In conclusion, in our ambulatory elderly hypertensive patients without clinically evident dementia, we found that a high plasma PTX3 level, particularly in those with high 24-hour BP levels, was a valid predictor of mild cognitive impairment. Because cognitive impairment increases the risk of both cardiovascular-related and noncardiovascular-related morbidity and mortality and also impairs the quality of life in elderly persons, our data have important clinical implications for identifying elderly individuals most likely to develop cognitive impairment. A follow-up study will be needed to establish a causal relationship between inflammation and the cognitive decline, and future studies to elucidate the mechanisms through which inflammation is associated with cognitive impairment and intervention studies to determine whether treatment of inflammation and hypertension prevents cognitive impairment are also warranted.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found at: http://biomed.gerontologyjournals.org/

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