学 位 論 文 の 要 旨

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学 位 論 文 名　Pulse Pressure is Associated With Cognitive Performance in Japanese Non-demented Population: A Cross-sectional Study

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論 文 内 容 の 要 旨

INTRODUCTION

Pulse pressure (PP) is calculated as the difference between systolic (SBP) and diastolic blood pressure (DBP) and is considered as a measure of arterial stiffness. Vascular risk factors, especially hypertension, are known to be related not only to cardiovascular disease but also to cognitive impairment. Since hypertension is a major risk factor for cerebrovascular disease, it may also be associated with dementia. Given that PP is a better clinical indicator of functional arterial changes than BP itself, it might be related to the pathogenesis of cognitive impairment. In this study, we evaluated the associations between PP and cognitive function in a well-characterized Japanese health examination cohort.

MATERIALS AND METHODS

We studied a total of 2,546 individuals with a mean age of 60.8 ± 10.3 years. The assessment included medical history (hypertension, diabetes mellitus, dyslipidemia 1,386 men and 1160 women), neurological examination, BP measurement, neuropsychological

testing, and magnetic resonance imaging (MRI) scans of the head. We studied the relationship among cognitive function, brain infarction, cerebral microbleeds (CMBs), periventricular hyperintensities (PVHs) and white matter hyperintensities (WMHs). General cognitive function was assessed using Okabe's Intelligence Scale (Okabe's test), The Kohs' block design test (Kohs' test), the frontal assessment battery (FAB), the Self-rating Depression Scale (SDS), and the Japanese version of the Apathy Scale.

We divided all subjects into high and low PP groups with a pre-defined cut-off value of 65 mmHg. To avoid possible confounding effects caused by grouping with PP values, we used propensity score matching in this study. To obtain the propensity score, we assigned these two groups to the explanatory variable and performed a logistic regression analysis. Physical examination results, silent brain lesions, and cognitive functions were compared between the high and low PP groups. To evaluate whether the association between PP and cognitive function was affected by SBP, mediation analysis was performed. In the mediation analysis, the significance of the effect was tested using Sobel's delta method. The study protocol was approved by the Research Ethics Committee of Shimane University (No. 20160217-1).

RESULTS AND DISCUSSION

Among 2,546 participants, 439 (17.2%) were in the high PP group. The propensity matching algorithm produced 433 pairs of patients with similar propensities. In the propensity-matched sample, there were no significant differences in the occurrence of silent lesions between the two groups. The Okabe scores and Kohs' scores were still lower in the high PP group than in the low PP group. In mediation analysis, the direct effect of PP on Okabe's test was significant, while the SBP mediated effect of PP on Okabe's test was not significant. Similarly, the direct effect of PP on Kohs' test was significant, while the SBP mediated effect of PP on Kohs' test was not significant. Thus, PP was significantly associated with Okabe's and Kohs' tests, but was not mediated by SBP.

In this study, it was revealed that higher PP was associated with lower cognitive performance. Furthermore, our results indicate that these relationships were not mediated by SBP. However, we observed no significant relationship between PP and silent brain lesions. To date, studies on the association between PP and cognitive function have shown inconsistent results, stemming mainly from the difference in age of the study populations. The subjects, who participated in our study, were individuals with an average age of 60 years; therefore, in this study, the impact of PP on cognitive performance of middle-aged populations was focused. Recently, consistent with our study, the previous study on 3009 subjects from the SPRINT-MIND revealed that higher PP was associated with poor

cognitive performance. Similarly, another study in a total of 3129 subjects from the Third National Health and Nutrition Examination Survey revealed that higher PP was associated with worse MMSE (Mini-Mental State Examination) performance. On the other hand, studies in very old individuals oppose the findings of this study. The previous study demonstrated that higher PP related to better cognitive function in a cohort of 476 participants aged 85 years or more. Further studies are needed to evaluate these age-dependent differences in the relationship between PP and cognitive function.

Interestingly, the relationship between PP and Okabe's and Kohs' tests was not mediated by SBP, even though SBP was strongly associated with PP and was previously linked with cognitive dysfunction. PP could be a surrogate marker of arterial stiffness that represents the chronic effects of hypertension other than BP itself. Our results are consistent with previous reports showing that PP was a better predictor of cognitive impairment than BP. Thus, hypertension-associated changes in the brain might be detected by measures of arterial stiffness, such as PP, rather than SBP. In this study, PP was not associated with the prevalence of silent brain lesions, including SBI, PVH, SWML, and CMBs, indicating that PP might affect cognitive function independent of the burden of arteriosclerotic cerebral small vessel-related lesions. In previous reports, the relation between arterial stiffness and the amount of Aβ deposition in the brain was suggested. A previous study revealed that arterial stiffness measured with peripheral pulse wave velocity significantly associates with the extent of Aβ deposition and the accumulation of Aβ in the brain over 2 years in elderly adults without dementia. Since an increase in PP is recognized as arterial stiffness, it is speculated that increased PP causes decreased flow of brain interstitial fluid, thereby leading to decreased Aβ clearance along the perivascular space and accelerating the formation of Aβ plaques. This study has several limitations. First, the cross-sectional study design limits causal inferences. Second, the subjects were recruited from a health examination cohort that might not properly represent the entire population of Japan. Finally, the association between cognitive performance and brain lesions was not evaluated.

CONCLUSION

In conclusion, our findings suggest that PP has a significant relationship with cognitive function among non-demented Japanese individuals. Future longitudinal studies are needed to explore the association between PP and cognitive decline in a representative sample of the Japanese population.